DEC 30 1912

VOL. CXLV, No. 1 JANUARY, 1913 No. 490

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

EDITED BY GEORGE MORRIS PIERSOL, M.D.

LIBRARY OF CONGRESS DEC 31 1912 COPYRIGHT ENTRY

THE THEORY AND TREATMENT OF DIABETES. By CARL VON NOORDEN, M.D. . . . 1

EXTRACARDIAC CAUSES OF FAILURE OF COMPENSATION IN VALVULAR DISEASES OF THE HEART. By ALFRED STENGEL, M.D., Sc.D. 17

THE KINETIC THEORY OF GRAVES' DISEASE. By GEORGE W. CRILE, M.D. . . . 28

THE COMMONER FORMS OF RENAL DISEASE, WITH SPECIAL REFERENCE TO THE KNOWLEDGE OF THEM MOST USEFUL AT PRESENT TO THE GENERAL PRACTITIONER. By LEWELLYS F. BARKER, M.D. 42

THE INFLUENCE OF EXERCISE ON THE HEART. By R. TAIT McKENZIE, B.A., M.D. . 69

OBSERVATIONS ON A CASE OF MEDIASTINOPERICARDITIS TREATED BY CARDIOLYSIS (BRAUER). By ARTHUR D. DUNN, M.D., and JOHN E. SUMMERS, M.D. . 74

THE RELATION OF PARASITIC AMŒBÆ TO DISEASE. By CHARLES F. CRAIG, M.D. . 83

BREAST TUMORS, WITH SPECIAL REFERENCE TO CARCINOMA. By A. PRIMROSE, M.B., C.M., M.R.C.S. 100

THE RELIEF OF GASTRIC CRISES IN TABES DORSALIS BY RHIZOTOMY. By CHARLES H. FRAZIER, M.D. 116

A CASE OF ALKAPTONURIA. By HELEN BALDWIN, M.D. 123

OWNERS AND PUBLISHERS

Philadelphia LEA & FEBIGER New York

COPYRIGHT 1912, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, FIVE DOLLARS A YEAR, POSTPAID

Important New Work **Ready in a Few Days.**

MEDICAL MEN AND THE LAW

A MODERN TREATISE ON THE LEGAL RIGHTS, DUTIES AND LIABILITIES OF PHYSICIANS AND SURGEONS

By HUGH EMMETT CULBERTSON, Esq.

Member of the Ohio and New York Bars; Contributing Editor to many legal publications

---

Most medical men enter upon practice with perhaps a general sense of responsibility, but with no knowledge at all of their myriad rights, duties and liabilities as viewed by the law. No matter what his professional qualifications may be, a physician lacks the armor of self-protection if he fails to understand the reciprocal obligations between himself and the public. The penalty is commensurate with the responsibilities attaching to his profession, which deals with issues of life and death. The body of law covering all the relations between the physician and the public is very definite, but it has never before been gathered into a comprehensive, clear and authoritative statement. This book deals not only with regular medicine and surgery, but also with the legal aspects of all the other methods of healing which are practised at the present time. Every medical man who values his own peace of mind and material welfare will find this work replete with information of the utmost practical importance.

New (7th) Edition **Just Ready** **Thoroughly Revised**

A PRACTICAL TREATISE ON

FRACTURES AND DISLOCATIONS

By LEWIS A. STIMSON, B.A., M.D., LL.D.

Professor of Surgery in Cornell University Medical College, New York City.

Octavo, 930 pages, with 459 engravings and 39 full-page plates. Cloth, $5.00, net.

When a book on any scientific subject reaches its seventh edition, that fact alone proves that it is needed by those for whom it is written. Dr. Stimson has long been recognized as the greatest living authority on fractures and dislocations, and his book has been acknowledged, since the publication of the first edition, to be the most complete and satisfactory treatise on these subjects in the language.

This new edition has been enriched by important additions on the subject of treatment, especially of old dislocations and in respect to the operative treatment of recent fractures. Several new sections have been included in this edition, and over one hundred new illustrations have been added.

To the surgeon the work should be valuable because of its high authority; to the practitioner it should be indispensable, because, even if he does not take surgical cases, he frequently finds it necessary by reason of their urgency to treat these injuries; and to each it should be particularly acceptable because both of these allied subjects are considered between one pair of covers, and at a very moderate cost.

PHILADELPHIA
706-8-10 SANSOM ST.

LEA & FEBIGER

NEW YORK
2 WEST 45TH ST

CONTENTS

ORIGINAL ARTICLES

The Theory and Treatment of Diabetes 1

By Carl von Noorden, M.D., Professor of the First Medical Clinic in Vienna, Austria.

Extracardiac Causes of Failure of Compensation in Valvular Diseases of the Heart 17

By Alfred Stengel, M.D., Sc.D., Professor of Medicine in the University of Pennsylvania, Philadelphia.

The Kinetic Theory of Graves' Disease 28

By George W. Crile, M.D., Professor of Surgery in the Western Reserve University, Cleveland, Ohio.

The Commoner Forms of Renal Disease, with Special Reference to the Knowledge of Them Most Useful at Present to the General Practitioner 42

By Lewellys F. Barker, M.D., Professor of Medicine, Johns Hopkins University, and Physician-in-chief, Johns Hopkins Hospital.

The Influence of Exercise on the Heart 69

By R. Tait McKenzie, B.A., M.D., Professor of Physical Education in the University of Pennsylvania, Philadelphia.

Observations on a Case of Mediastinopericarditis Treated by Cardiolysis (Brauer) 74

By Arthur D. Dunn, M.D., Professor of Medicine in the John A. Creighton Medical College, Omaha, and John E. Summers, M.D., Omaha, Nebraska.

The Relation of Parasitic Amœbæ to Disease 83

By Charles F. Craig, M.D., Captain, Medical Corps, U. S. A., Washington, D. C.

Breast Tumors, with Special Reference to Carcinoma 100

By A. Primrose, M.B., C.M. (Edin.), M.R.C.S. (Eng.), Associate Professor of Clinical Surgery, University of Toronto; Surgeon to the Toronto General Hospital.

The Relief of Gastric Crises in Tabes Dorsalis by Rhizotomy 116

By Charles H. Frazier, M.D., Professor of Clinical Surgery in the University of Pennsylvania, Philadelphia.

A Case of Alkaptonuria 123

By Helen Baldwin, M.D., New York City.

REVIEWS

The Anatomy of the Human Eye as Illustrated by Enlarged Stereoscopic Photographs. By Arthur Thomson, M.A., M.B., F.R.C.S. . . . 129
The Practitioner's Visiting List for 1913 130
Pleurisy. By Alex. James, M.D. 131
Infant Feeding. By Clifford G. Grulee, A.M., M.D. 132
A Text-book of Obstetrics. By J. Whitridge Williams, M.D. . . . 133
A Collection of Papers Published Previous to 1909. By William J. Mayo and Charles H. Mayo 133
Trépanation Néolithique, Trépanation Pré-colombienne, Trépanation des Kabyles, Trépanation Traditionelle. Par le Dr. Lucas-Championnière 134
Further Researches into Induced Cell Reproduction and Cancer. By H. C. Ross 135
Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, Rochester, Minnesota, 1911 136

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D., AND ROGER S. MORRIS, M.D.

The Wassermann Reaction in the Rabbit 137
The Histological Disappearance of Skin Syphilides under Salvarsan . . 137
The Histological Structure of Syphilitic Lesions in the Rabbit . . . 138
Recent Modifications of the Romanowsky Stain 138
Clinical Experience with Neosalvarsan 139
Perpetual Arrhythmia 139

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D., AND T. TURNER THOMAS, M.D.

The Treatment of Nevi, Based on More than 2000 Cases 140
A Study of Sprain Fracture as an Essential to the Occurrence of Dislocation 140
Operation for Pneumatocele of the Parotid Gland and Stenson's Duct (Glass-blower's Tumor) 141
A Contribution to Surgery of the Heart 142

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.

The Production of Active and Passive Immunity to the Pneumococcus with a Soluble Vaccine 143
The Duration of Immune Bodies in the Blood after Antityphoid Inoculation 143
The Administration of Salvarsan in Syphilis 144
The Effect of Benzol on Leukemia 144
Absorption of Food in Typhoid Fever 145
The Treatment of Leukemia with Benzol 145

PEDIATRICS

UNDER THE CHARGE OF

LOUIS STARR, M.D., AND THOMPSON S. WESTCOTT, M.D.

The Cutaneous Reaction to Tuberculin in Childhood 146
Pneumococcal Infection in Infancy and Childhood 147
The Dietetic Treatment of Purulent Affections of the Urinary Tract in Children 147

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

The Effect of Chloral Hydrate upon the Liver and Kidneys 148
Fever in the Newborn 148
Induced Labor for Pelvic Contraction 149
Cleidotomy 149

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.

Menorrhagia of Puberty 150
Lactation Associated with Ovarian Carcinoma 151
Lactic Acid Therapy in Gynecology 152

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

AND

T. B. SCHNEIDEMAN, A.M., M.D.

On Ocular Palsies Occurring as the Sole or Most Conspicuous Evidence of Disease 152
Pathogenesis of Glaucoma 153
Voluntary Nystagmus 154

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.

Hypogenetic Nephritis 154
Tumors in Cold-blooded Animals 155
A New Recorder in Wireless Telegraphy 155
Changes in the Liver after Parathyroidectomy 155
Comparative Toxicity of Methyl and Ethyl Alcohol 156
The Lesion in Whooping Cough 156
The Serum Diagnosis of Echinococcus Infection 156

CLB261634

THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JANUARY, 1913

ORIGINAL ARTICLES

THE THEORY AND TREATMENT OF DIABETES.[1]

By Carl von Noorden, M.D.,
PROFESSOR OF THE FIRST MEDICAL CLINIC IN VIENNA, AUSTRIA.

I propose to present in broad outline the altered conditions of metabolism which occur in diabetes mellitus, and also to point out some of the indications for treatment which scientific investigations upon the metabolic disturbances have revealed.

The human body obtains its energy and nutrition from three types of foodstuffs: proteins, fats, and carbohydrates. For general purposes of work, warmth, and nutrition all three groups serve well; the muscular tissues are, however, more specific in their requirements. The working cells of the muscles do not utilize each type of foodstuff alike; they find the sugars the most useful for their energy production. It is possible, but not very probable, that they can use other materials for the same purpose, but this in too slight an extent to make the substitution of any practical importance, and we may, therefore, for the present leave this possibility out of our calculations.

As the working cells of the body use the sugars as their foodstuff and immediate source of energy, it is necessary that a mechanism should exist that renders the sugar always available for this purpose. The liver fulfils this function. The liver supplies the sugar in such a way that the arterial blood streaming to the tissues maintains an average sugar content of 0.75 to 0.85 sugar per 1000 parts of blood. The demands of the tissues for sugar

[1] Read before the Leland Stanford, Jr. University Medical School, San Francisco, and at the Johns Hopkins University, Baltimore. The questions mentioned in this paper are quoted in full in the author's book, *Modern Aspects of Diabetes Mellitus, its Theory and its Treatment*, New York.

vary to a large extent. During active muscular work they require four or five times as much sugar as when at rest. The liver responds to these needs by producing more or less sugar as occasion demands; the sugar requirements of the tissues determine the amount of sugar the liver is to produce. If this is put into commercial phraseology it might be said that supply and demand balance exactly. The maintenance of the sugar content of the blood is one of the most important functions of the liver. If the liver produces more sugar than the tissues require there is an abnormal amount of sugar present in the blood (hyperglycemia), and some of it escapes through the kidneys into the urine. On the other hand, if the liver does not manufacture sufficient sugar, the muscles suffer and signs of fatigue occur, because the working cells are insufficiently supplied with food. Such a condition appears during long-continued, strenuous muscular work. Then the need for sugar is so enormous that the liver is unable to meet the demand rapidly enough. The sugar content of the blood falls and severe fatigue and lack of energy appear.

In examining the sugar factories of the body—the liver cells—it will be found we have to deal with a complicated mechanism. It is well known that all the carbohydrates of the food are converted into sugar in the intestines and are carried to the liver in this form. It is only at certain times of the day when large quantities are being taken that carbohydrates are consumed and absorbed. If this quantity of carbohydrates simply passed through the liver there would result an excess of sugar in the blood; the sugar would not be completely used up, and a large part would be caught by the kidneys and excreted in the urine. This actually happens if healthy individuals eat large quantities of sugar. The condition thus produced has been termed "alimentary glycosuria."

A special form of protection, however, exists for the prevention of this excessive flow of sugar into the blood after a large meal of carbohydrates. The liver takes up the sugar as soon as it arrives and stores it in its cells. In order that the easily soluble sugar may be retained in the cells it is instantly changed into an insoluble form known as "glycogen." This glycogen is a reserve material. The liver conserves any overplus of sugar in this way so that any demands may be instantly met. In order to enter the circulation, however, the glycogen must be changed again into a soluble form, for as glycogen it cannot be transported *via* the blood to the muscles. To this end a ferment called diastase is provided. It is present in the liver in large quantities, although it occurs also in all the other organs and tissues. Diastase is widely distributed; it occurs in plants as well as in animals. It plays an important part in the nutrition of young plants in converting starch into sugar, just as it provides the blood with sugar for the muscles.

This storage of carbohydrates in the form of glycogen and the

further change of glycogen into sugar is not all that the liver can do. Human beings consume various kinds of foodstuffs, and they are not always able to obtain sufficient carbohydrates to meet the requirements of the body. Therefore, the organism is compelled to form sugar from other materials.

Albumins and fats are available for this purpose; proteins are considered as reserve materials of the first order and fats as reserves of a second order. The two substances play different parts. The albumins do not yield much sugar, but they act as strong irritants of the sugar-forming apparatus. When the liver cells break up the protein they are forthwith stimulated to form carbohydrate; the sugar formed from the albumin passes into the general circulation; thus it shares the same fate as sugar which as such reaches the liver with the food.

Fats act in another way. They form a rich source for carbohydrates. In those who consume small quantities of carbohydrates, and also in those who eat an average mixed diet, there is considerable formation of sugar from fat, for few people eat as much carbohydrate as their tissues require. Fat does not stimulate the sugar-forming apparatus in the liver; the hepatic cells use fat for this purpose only when other materials fail. Carbohydrates and proteins dictate the work of the sugar-forming apparatus; while fat, on the other hand, is the self-selected material of this apparatus.

It has been shown that the liver is the sugar-forming organ of the body. The diastatic ferment is a peculiarly active substance, which is not directly concerned with the demands of the tissues for sugar, and is somewhat of a menace to the glycogen content of the liver. If not checked it would furnish to the blood all the sugar-forming material that is brought to the liver, so that the blood would be either too rich or too poor in sugar. It is a fact that such an irregularity of the sugar factor occurs under certain conditions of disease. Healthy people, however, exhibit a perfect balance between sugar needs and sugar production; care is apparently taken that the diastatic ferment does not decompose more glycogen (that is, does not furnish more sugar) than is necessary to maintain the normal level of the sugar content of the blood. The exact chemical processes by which this is brought about are still unknown. It is not clear whether it is a physical or chemical property of the liver cells by which the action of the diastatic ferment is depressed or increased, nor do we know the nature of the signal which indicates to the liver cells the immediate needs of the tissues for sugar. However, many interesting facts have already been discovered.

One of the most important of them is the recognition that the liver is not so independent in its management of the sugar production as was at one time thought. There are at least two controllers which influence the intensity of the sugar-forming processes to a high degree; they both act as antagonists.

The pancreas is the first regulator to be considered. The blood from the pancreas passes to the liver and contains a specific product of the pancreatic cells (called an internal secretion), which exerts a retarding influence upon sugar production. If the pancreas be removed from the body this influence is also removed, and the amount of sugar produced in the liver is greatly and irregularly increased. Each type of material from which sugar can be produced becomes grist to the mill, and enormous quantities of sugar pass into the blood stream and raise the sugar percentage to an abnormal height, while a large amount escapes from the body in the urine. This is practically a severe type of diabetes. Clinical experiences show that diminished activity of the pancreas is the cause of a large number of cases of diabetes. This altered power of the pancreas is chiefly one of weakened function; there are not always anatomical changes in the structure of the gland. There are all grades of pancreatic insufficiency, and, dependent upon the condition of the pancreas, the disturbance of the regulation of the sugar processes is either intense or slight. It may vary considerably from time to time in the same case.

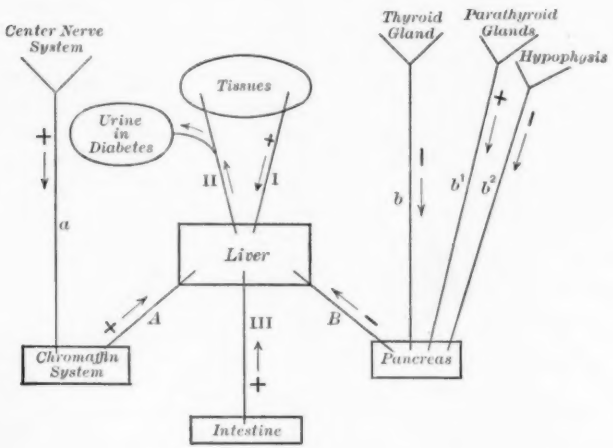
The other regulator is the suprarenal gland system. Minute quantities of adrenalin are being continually produced by this system and pass into the blood. This interesting substance possesses the property of exciting the sugar production in the liver to a high degree. As a rule the injection of about 1 milligram of adrenalin under the skin or into a vein will cause the excretion of sugar in the urine of an adult man within a quarter of an hour, which may continue for several hours. Experiments upon animals have shown that if the injections be repeated daily there is a regular response in the shape of urinary sugar, but the quantity gradually diminishes, and finally ceases to appear unless the dose of adrenalin be increased. The suprarenal, therefore, antagonizes the action of the pancreas so far as regards the regulation of sugar production. The one inhibits and the other stimulates the formation of sugar. The normal organism maintains its regulation of sugar production and output through the equilibrium that exists between these two agencies. Strong stimuli emanating from one organ may be compensated by increased action on the part of the other one. This has been proved by numerous experiments: In the beginning, injections of adrenalin, or an increased function of the gland itself, both excite the liver markedly. The pancreas, surprised, as it were, at the vigor of the irritant, is not able at the moment to avert the danger; it has to allow the undue increase of sugar production to have its sway. After some days, however, the repeated stimulation forces the pancreas to throw off its inertia and to oppose the action of the adrenalin. The antagonism between the two glands and their compensatory relations may be demonstrated by experiments.

However, neither of these two controllers of the sugar manu-

factories are able to act entirely independently. Their activities are influenced by forces external to themselves. This is especially the case with the suprarenals, which developmentally and functionally are directly under the control of the nervous system—the sympathetic nervous system acts as an intermediary between the central nervous system and the glands. The exact area of the nervous system which exercises this power is situated at the junction of the brain and the spinal cord. This well-known fact was discovered by Claude Bernard. The glycosuria which results from the puncture of Claude Bernard's centre in the medulla is due to the action of the central nervous system upon the suprarenal glands *via* the sympathetic nerves; adrenalin is at once formed in larger quantity, passes into the blood, and stimulates the sugar production in the liver. This "piqûre" glycosuria is practically the same as suprarenal glycosuria. It has been found, also, that nerve injuries of different kinds, and also many poisons, lead to the appearance of glycosuria. In all these instances it is a question of reflex or toxic irritation, which excites Claude Bernard's centre, with the subsequent excess formation of adrenalin and stimulation of the sugar-forming tissues. At the first appearance these observations seem to show that a considerable number of cases of diabetes are due to similar nervous causes (neurogenous diabetes). However, in spite of all this and many other findings it is still not yet clear whether there exists a chronic form of diabetes which only arises from neuropathic or suprarenal sources. There is no doubt but that the nervous system and the suprarenals play an important part in those acute rapid forms of glycosuria which are associated with psychical, nervous, cerebral irritations or with acute toxemias, and which often disappear entirely. They play also a definite part in chronic diabetes; cases are often seen in which the glycosuria increases as a result of nervous irritation or cerebral overstrain apart from any influence of the food consumed. In almost every case of diabetes it is possible to distinguish a nervous and an alimentary factor. However, the glycosuria may only be considered as purely neurogenous, when it is transitory and if it is perfectly independent of any foodstuff. But, if the glycosuria reappears after transitory psychical or nervous attacks, and if during these phases the composition of the food exerts any definite influence upon the appearance or disappearance of the glycosuria, then we may not regard the condition as a genuine neurogenous diabetes, but must think of some concurrent diminished activity of the pancreas. For the "nervosity," that is, the hypersensitiveness of the nervous centres and paths, does not alone suffice to explain the condition; otherwise, neurasthenics would, as a rule, show tendencies to glycosuria. This is, however, not the case; the greater number of neurasthenics are not glycosurics even if they present other signs of irritation of the sympathetic system.

Neither does the pancreas work independently: Its energies may be influenced from outside. We now come in contact with the properties of the thyroid gland. The thyroid secretes chemical substances which it passes into the blood. These are the same substances which are sometimes used in obesity. An overproduction of the thyroid secretion paralyzes the action of the pancreas; pancreatic vigilance over the hepatic functions becomes diminished, and so in cases of voluntary thyroidal overproduction (Graves' disease) or after administration of thyroid extract the urine may contain sugar. For this reason great care should be used in employing thyroid extract. On the other hand, the pancreas becomes more energetic and powerful when the thyroid gland secretion is diminished, as in myxedema, cretinism, and thyroid ablation. In these diseases, no matter whether large amounts of sugar are given or the suprarenals send out increased stimuli, glycosuria does not occur. The pancreas reacts most probably to other influences also, but accurate information about these is not yet available.

We see, therefore, that the work of the sugar factory is a complicated process. Perhaps the mechanism may be put more clearly in the form of the accompanying diagram.



The manufactory for sugar is the liver, and the liver cells constitute the working department.

The important claims that *determine* the amount of the sugar production arrive from other organs and tissues, especially from the muscles (path *I*). The greater the consumption of sugar the stronger will be the claiming impulse, and an amount of sugar sufficient

to meet the demand will pass into the blood (path *II*). This is normally the only influence which induces the liver to raise its output.

However, along path *III* stimuli will also pass. This path represents the blood streaming into the liver from the intestinal wall, and carrying carbohydrates and the products of protein digestion. The quantity of these materials varies according to the type and composition of the food. So long as the manufacture of sugar is well under control the effect of this form of stimulus is not to induce a liberal outpouring of sugar into the general blood stream, but to form glycogen. This glycogen is then stored until it is reconverted into sugar at the request of the tissues, and travels along path *II* to the muscles, etc.

In order to maintain the excitability of the sugar manufactories at the proper intensity the two controlling factors come into play. The pancreas, which depresses the excitability, sends its secretion along path *B*, while the suprarenals, which increase the excitability, distribute their secretion along path *A*. This conjoined action serves to keep the process in equilibrium.

Both these controlling glands are in turn influenced by other organs—the pancreas through the thyroid gland path (*b*) and the suprarenal through the nerve paths (*a*). The diagram shows still other influences (path b^1 and b^2); their existence is most probable, but their origin is undetermined. They seem to be subordinate in importance and action.

A consideration of the diagram and its explanation should lead to the conclusion that the excretion of sugar in the urine is not indicative of one disease alone. Of course, under all circumstances the glycosuria is a sign of increased production of sugar and an excess of sugar in the blood stream. Even if only traces of sugar are found in the urine it is evident there is an excess present in the blood.

The cause of the disturbance may be found in various places, but in the case of real diabetes several sources are of unequal importance.

1. Primary disease of the liver itself: This in reality plays a subordinate role. In some diabetics the liver is enlarged, but it is an hypertrophy resulting from overwork; the cells themselves are healthy. In primary disease of the liver, glycosuria is the exception, not the rule. If disease of the liver and diabetes occur in one and the same individual the two conditions appear independently.

2. Primary anomaly of the instreaming impulse along path *I*, that is to say, a demand for more than the actual needs of the tissues: This is theoretically possible. It plays an undoubted part in the form of diabetes due to phloridzin poisoning. This is, however, of experimental interest only. Such an intoxication does not throw any light upon the etiology of human diabetes, and

there is not a symptom indicating that overpowering impulses along path I may start human diabetes.

3. There may be an increased flow of sugar from the intestine along path *III*, which gives the glycogen-forming function of the liver too much to do and the untransformed sugar passes into the blood (transitory alimentary glycosuria). The normal powers controlling the sugar-producing factories are so high, however, that under ordinary conditions only an excessive quantity of sugar is too much for them, and some escapes into the blood stream. Should sugar appear in the urine of an adult upon an average sugar and starch diet it would be wrong to regard it as a physiological or harmless glycosuria. On the contrary, it should be regarded as an indication of a disturbed sugar mechanism and a slight form of diabetes. I mention this intentionally, because the term "alimentary glycosuria" has led to regrettable and costly errors. With this term many doctors console their patients, and many patients comfort themselves, especially if the glycosuria occurs only occasionally, and then disappears for a while in spite of liberal intake of carbohydrates. Such a fluctuation of the condition is not an exception in the early stages of diabetes; in fact, it is rather the rule than otherwise. This is the stage, moreover, in which rigorous treatment should be undertaken, for at this stage diabetes may often be cured. If the warning signal is not observed, the disease, in the majority of cases, progresses consistently, and then it is too late to realize that the consolation was ill-founded, and that in the past the patient has wasted both time and opportunity.

4. The anomalies connected with path *A* have already been stated. The disease may be in the suprarenal itself or in the course or head station of the line *a;* disturbances may also arise in the head station at Claude Bernard's centre. The number of the neurogenous glycosurias and the toxogenous glycosurias belong to this group as well as the increased excretions of sugar in diabetes under the psychical irritation. However, it is unlikely that influences passing to the liver by path *A*, or path *a*, ever develop more than a transitory effect or at any time produce a chronic form of disease like diabetes. There is more to be said against it than for it.

5. In human diabetes, both in slight and severe cases, the anomalies of path *B* are by far the most important, it may be that either the pancreas itself is diseased and functioning badly or that its energies are paralyzed by outside influences (paths b, b^1, b^2, and their head stations). The effect of the *b* line stimuli is, however, not of marked importance in most cases of human diabetes. More frequently it happens that the chief disturbance is localized in the pancreas itself and that the impulses, passing down the *b* lines, irritate it only occasionally.

These considerations emphasize the view that diabetes is a complicated disease and show how little aid can be rendered to the patient if the attention is focussed upon the glycosuria alone. The condition demands that the functional powers of all the organs of the body be considered. In order to discover in a case of diabetes the extent of the anatomical and physiological disturbances and the effect of distant organs upon the sugar production a knowledge of physiology and pathology is necessary Each case is a law unto itself, and marked variations from a common type often occur.

However, no matter where the primary disturbance is localized, or whether one or more of the controlling factors are acting abnormally, in diabetes there is always present an enormous irritability of the *sugar-forming apparatus of the liver;* normal impulses are responded to, not with an ordinary output of the required sugar, but with an extraordinary, almost unlimited sugar production. This lack of coördination between the intensity of stimulus and extent of response is the characteristic feature of the disturbances of metabolism in diabetes. Naturally, there are considerable gradations; at one end the hypersensitiveness of the sugar-forming apparatus is only slight, and is only revealed when the overstraining is specially intense; at the other end the hypersensitiveness manifests itself even to the slightest stimuli. In fact, it is the extent of difference between stimulus and response which determines the severity of the diabetic process.

Marked sensibility of the sugar-forming apparatus and increased production, at once incommensurate and objectless, leading to large losses of sugar, become manifest in each stage of diabetes. All the stimuli which experimental investigation has shown to act as irritants to sugar production exert an increased influence in diabetes: such as the instreaming of carbohydrates and the digestive products of proteins into the liver; acceleration of general metabolic processes by excessive and tiring muscular work or acute febrile attacks; psychical and other nervous excitations; injections of adrenalin; thyroid gland feeding, etc. But these factors do not act equally in every case; from what has been said about the manifold varieties of the stimuli, this will be readily understood.

A recognition of the great excitability of the sugar-forming apparatus and of its tendency to excessive sugar production, as the characteristic features of diabetes, facilitates the appreciation of the problems and aims of a rational form of treating the disease. There is urgent need to calm the excessive irritability of the sugar mechanism. Every unnecessary burden must be avoided. If we are able, by a wise choice of food and the exclusion of other irritants, to lower the demands upon the sugar manufactories the sugar production in slight cases will keep within normal limits, almost without exception, and the glycosuria will disappear. The diabetes

is not cured entirely, for if there again is any overworking of the manufacturing centres they will at once, or in a short time, get out of order. However, the new conditions make for healing or for at least a real and long-lasting improvement. Beyond this Nature herself must make the necessary provision. We have to deal with an every-day experience; if the heart is defective and responds to extra work with rapid or irregular contractions, we protect the heart from added burden; we advise an avoidance of overexertion and overemotion, and then by degrees—if the heart through being spared regains its powers—we gradually and carefully increase the demands for work under close supervision. In this way many hearts regain a normal capacity. Similar examples might be brought forward from the conditions of overstimulation and overstrain of the nervous system, gastric and intestinal diseases, renal diseases, and injury or inflammation of the extremities. In these and other diseases it is necessary to rest the damaged organs. In diabetes, however, this is the exception rather than the rule. The development of the diabetic therapy supplies, perhaps, the explanation. But there are other forces at work also. The patient with heart disease or stomach trouble or injuries to the feet, feels at once when he has overworked the organ; every careless action is followed by a resultant warning pain. The diabetic patient, however, does not feel or recognize the result of the overworking of his sugar mechanism. Only intelligent individuals understand that nervous alteration indicates an overplus of sugar in the blood. A continued daily examination of the urine would supply such an indication, but this would not be possible except in sanatoria or hospitals, and then is of value only if the physician takes into consideration the total sum of impulses which govern the sugar formation (namely, quantity and quality of food, extent of bodily and mental work, presence or absence of complications, etc.). With the usual analysis, once every two weeks or two months, a systematic control is practically impossible. Thus it is too often the case that the organs of the diabetic are overstrained and call for a protective therapy without his being aware of the fact. He feels himself perfectly well. This lack of discomfort as a momentary result of excessive overloading is characteristic of diabetes. The danger lies in the future.

As a rule, the patient does not fully avoid the excessive overloading; there follows a marked irritation of the sugar mechanism; the urine may even still not show sugar to an ordinary analysis, but every such transitory stimulation increases the sensibility of the organs in the future. The more frequently this overloading be repeated the greater will be the difference between the strength of stimuli and the amount of response. Bread and other meal foods which were taken well at first later lead to glycosuria, or, in other words, a slight diabetes shows definite progression. In

addition other disturbances arise, chief of all the formation of acetone and associated substances. This relates to anomalies of the metabolism of fat. Normally, the fat of the tissues is burned to carbon dioxide and water. If, however, during an excessive production of sugar each atom of carbohydrate is removed from the liver as rapidly as it is formed, then the chemical process connected with the cleavage of the fat molecule assumes another type, and acetone bodies result. When large quantities of these are formed there is produced a new danger for the tissues. The presence of carbohydrates (particularly glycogen) is necessary for the cleavage of fat to follow its proper course. It is evident, therefore, that increase of carbohydrates in the food will deal with acetone formation by providing the necessary amount of protective carbohydrates. The worst cases excluded, this certainly leads to the desired end; but it has proved a dangerous type of therapy. The additional carbohydrates constitute an exceedingly strong excitor of the sugar mechanism and damage its regulation more and more. The way to combat the process is to protect the sugar mechanism by sparing its work—by systematic diminution of the carbohydrates as well as of the irritating protein material. Then the excited sugar formation and the acetone bodies decrease. I shall not now enter into the complicated question of the relation of acetone formation to the type of dietary, contenting myself with the remark that this question has assumed too great an importance in the eyes of those in daily practice. To a certain degree acetone formation in diabetes is not at all dangerous. When treated properly it is easier to deal with the acetonuria than is generally supposed.

Since the altered relations between the intensity of the stimulus and the extent of the response show considerable gradations, we may assume that the means of treatment will also call for manifold variation. As a matter of fact, practically all the therapeutic methods find an application in diabetes. Far beyond all others, however, is the treatment by suitable dieting, because food is a factor which acts as a continuous daily renewed irritant of the sugar mechanism, now damaging it or conserving it according to its quantity or quality. The chief excitor among the foodstuffs is the carbohydrate, and its restriction, for more than a hundred years, after many aberrations, has always constituted the most prominent factor of diabetic therapy. The way in which this was done was made a hard and fast rule, and even today, I regret to say, for the most part the same holds true. The worst of these hard and fast rules is that every diabetic is subjected to practically the same restriction of the carbohydrates. The 60 to 80 grams of carbohydrates, which is the amount generally allowed, must in reality, be considered as 80 to 100 grams or more, since the instructions given to the diabetic are, as a rule, not sufficiently precise, and

errors are therefore unavoidable. For a certain number of diabetics 80 + 100 grams of carbohydrates per day is the proper amount, that is to say, the quantity with which the urine remains free from sugar. For the greater number of patients, however, this quantity is not suitable. It may be too high or much too high; or it may be too low or much too low. In both instances the result will be a damage to the tissues. If more carbohydrates are consumed than the liver can utilize in an ordinary fashion, the diabetic disturbances of metabolism increase more and more; in one case slowly, in another rapidly, but in all there is a persistent increase.

After the carbohydrates, there are the proteins to consider as irritants of the sugar mechanism. They pass direct to the liver and there undergo a further cleavage. By this means substances are produced which are transformed easily into sugar. The proteins are, therefore, to be regarded as sources of sugar, although the yield is not great; in fact, it is probably much less than the physiologist assumes. On the other hand, however, the proteins are powerful excitants of the liver cells, and are able to induce marked activity of the sugar-producing centres; in the healthy individual, whose sugar production is strictly controlled by the regulating organs, this excess of activity does not result. In diabetics, however, in whom the regulating apparatus is abnormal the response to these excitants is considerable. The effect of the proteins is not so much that of a source of sugar as it is that of a bellows upon a fire. It incites the sugar manufactories to an incommensurate and unbridled production. The various types of proteins exhibit this character in different degrees, while the hypersensibility of the diabetics to the irritant action of proteins in different cases also shows considerable variation.

The third important foodstuff—fat—does not exert any direct irritant action upon the sugar production. Fat, of course, is a source of sugar, but it plays a passive part, and is thus not comparable with the active powers of the carbohydrates and proteins; it is only used by the liver cells when other material is not at hand. Under conditions of marked excitation of the sugar mechanism, large quantities of fat are utilized and sacrificed. This explains the emaciation which comes on in severe cases of diabetes.

Alcohol is another material which acts as a food and does not irritate the sugar-forming process. On the contrary, it appears to diminish the formation of sugar.

The relations of the several fundamental foodstuffs to the sugar-forming processes in diabetes is thus apparently clear, but the problems of proper dietary are not yet fully solved.

In the foodstuffs used in the natural form or when cooked the fundamental nutrients are mixed in various amounts, and there are in addition other substances, such as alkaloids, acids, ethereal oils, etc. Apparently these compounds exercise an important

action upon the energy of the sugar-forming processes, so that it may happen that two foods which contain an equal amount of starch, and whose protein content does not vary materially, produce different effects when taken by diabetics. Investigations upon this question have not yet advanced to any great extent, but the fact is well recognized and possesses great interest from the standpoint of the nutrition of the diabetic; for instance, in oats there is apparently a substance which acts in such a way as to make oatmeal a better food for the diabetic than some other substances. Of course, certain precautions are necessary. Great heat destroys this substance, and its powers are not very apparent when oatmeal is taken at the same time as other meals or sugars or when the dietary includes meat proteins. Upon this discovery, made ten years ago, I based the so-called "oat cure" for diabetics, and, although the treatment is not applicable to all cases, many have derived benefit from it.

However, all the theoretical knowledge so far gained as to the influence of certain foodstuffs upon the sugar-forming processes does not permit the physician to cease his search for the correct dietary for each single case. It is invariably found that the general rules have to be modified to meet the individuality of the patient. The inexperienced physician only dares to prescribe average dietetic measures. The experienced doctor knows how easy it is by such means for damage to take place, and how important it is that the response of each diabetic to the quantity and quality of the food and to other factors should be ascertained before a plan of treatment is determined upon. This method, first instituted by the late E. Külz, and further expanded by B. Naunyn, I have worked out upon well-adapted lines and am able to recommend its wider acceptance. It is now recognized as the only correct dietetic method of treatment. How different this is from the methods of dietetics in this disease which prevailed in early days! Of 100 cases treated by the newer methods, scarcely 2 receive the same instructions, so various are the graduations and circumstances of each example of the disease.

For each patient there is only one correct method of treatment, and this must be sought for and found. A prolonged experience may make the search more easy, but the desired result cannot be obtained without systematic investigation and observation. For this purpose I generally take the patients into a sanatorium; it is important that the observations should be as exact as possible, for on the results depend the fundamental rules of proper living in the future. In no other way is it possible to avoid errors.

These investigations and a certain form of education or training of the patient are particularly important in the early stages of diabetes. It is a fatal error to assume that slight or occasional glycosurias may be neglected and that they do not call for means of defence.

This assumption is at the bottom of the meaning that diabetes is considered as an incurable disease which cannot be checked. This is not correct. Of course, there are cases of diabetes whose course cannot be checked by any kind of treatment; they are closely connected with a progressive change in the pancreas. Such examples occur chiefly in childhood; in the later decades of life they become more rare. Those cases that are originally simple and slight in type are rather frequent with elderly people. There is no question that the slight type of case may be kept harmless by the employment of a proper treatment. It is necessary, however, that every possible care be taken that the patient adopt a diet which permits him to keep free from glycosuria. This can nearly always be done. The extent of the restriction in food and drink that it is necessary to prescribe, as previously stated, varies considerably with each case. It is as important not to exaggerate the restriction as to be too yielding in the other direction. Should the case at once be led into the correct dietetic equilibrium, then the amount of the restriction and renunciation is not great. It is rather small compared with the advantage we gain and with the dangers we avoid. The loss of the sugar is only the least of the dangers. The chief one in such cases is the excess of sugar in the blood (hyperglycemia). This is always close at hand, even when the urine contains but traces. So long as there is too much sugar in the blood the tissues are subjected to a toxic action and evince a tendency to early malnutrition and disease. Other well-recognized and feared complications of diabetes, as arteriosclerosis, granular kidney, blindness, sciatica and other neuralgias, gangrene, etc., may be attributed to the same cause. They are the most frequent in those cases where slight glycosuria has been present for some years without being controlled. They could easily have been avoided in slight cases if the necessary care had been taken to regulate the intake of sugar-forming materials.

It is for the best interest of the diabetic to observe a strict regulation of the diet, and for a long time he must be careful what he eats and drinks. It would be much more convenient if there were drugs available which would act directly on the sugar mechanism or indirectly through the controlling organs (see diagram) and produce the effect which is attained by dietetic restrictions—namely, a calming of the useless activity of the sugar manufactories. The science of pharmacology teaches that the majority of drugs either excite or depress certain cell groups, such as glandular cells, nerve cells, muscle cells, etc. In the treatment of diseases of the heart, nervous system, digestive organs, etc., drugs prove to be of great value. But pharmacology has not provided any drug which acts directly upon the excitability of the sugar-forming process of the liver. To a certain degree opium is able to exert an influence in this way, but the administration of opium is associated with

so many drawbacks that its employment is much restricted. It is to be hoped that some harmless medicament may be found which will simplify the present dietetic treatment of diabetes. Its lack is the more regrettable, since in consequence of the poverty of scientifically recognized active drugs, many secret remedies and specialities are proclaimed as being specific in action and draw the overtrusting diabetic into their net. It is of interest to examine the grounds upon which the advocates of these remedies base their statements. The manufacturers and salesmen make it clear, either in print or verbally, that while the medicine is being taken the diet must be restricted and contain little or no carbohydrates. As a result the urinary sugar, of course, sinks at once; the chief factor, however, is the well-known dietetic regulation, while the lauded medicine plays only a subsidiary part, and serves—so to speak—as an advertising placard only. Later, the quantity of carbohydrates permitted is slightly increased, just as in scientific medical work, for the directions issued by the manufacturers are copied chiefly from medical handbooks. Perhaps they believe in the efficiency of their remedy rather than in the accompanying dietary. This, of course, is a mistake. There are some, nevertheless, who aim at misleading the public. It is evident that such treatment does not allow of a systematic application of the necessary dietetic restrictions; for this the manufacturer and his medical knowledge do not suffice. One does not find trained medical men giving their advice to such speculators. It is remarkable that some physicians fall a prey to the claims of these secret remedies; it is to be supposed that they do not understand the principles underlying the dietetic treatment of diabetes. It may be they learn that one of their patients is undergoing one of these cures; the prescribed diet happens to be the correct one for the patient, and the result fills the doctor with astonishment. The lack of his judgment and criticism lead him to accept the belief that something has happened which the scientific physician could not accomplish He is only right, however, in that he personally is unable to induce the result; and he is wrong and even blameworthy if he identifies his own capabilities with medical science. The only apology for his standpoint is that dietetic therapy in general and that of diabetes in particular demands a considerable amount of special knowledge, and that clinical instruction in this important matter was in the early days extremely poor, while there are even now many clinics in which there is much to be desired in this regard. The activity of the manufacturer and vendor of these specialities, and, on the other hand, the surrender of the patients to the mercy of these wonder cures, are to be regretted, because attention is diverted from the most important therapeutic factor (dietetic observances), or the restriction of the diet is simply on the lines

of hard and fast rules and not suited to the special requirements of each individual case. The dangers of the condition persist even if the pretended medicament consists only of harmless vegetable extracts.

It may occasion some wonder that mineral water cures are not here mentioned as a method of inducing a restriction of the sugar production. They stand in high esteem, and the great majority of patients place upon them much higher worth than that of regulating the diet. Karlsbad, Neuenahr, and Vichy are the chief favorites. The fame of these places could not be maintained if the patients did not derive some benefit from them. It is well known that the waters do not exert any demonstrable influence upon the production or excretion of sugar or upon the intensity of the diabetic processes. The value of a residence in these resorts lies in the fact that at least for a month the patients live, eat, and drink in a rational manner. In addition, the absence of the worry and irritation of every-day life tend to diminish the general nervous tension and to weaken the force of any irritating stimuli proceeding from the central nervous system to the organs concerned in the sugar mechanism. In the mild cases of diabetes there is also the favorable influence of the regular exercise, which is enjoined here, upon the glycosuria; in the severe cases the opposite effect may result. Many diabetics exhibit also certain complicating disturbances of the stomach, intestine, liver, kidney, etc., and upon these the mineral waters undoubtedly act in a favorable manner, and thus play a part in bringing about an increase in the general well-being.

If, on the other hand, the value and influence of the mineral-water cure be exaggerated, there is constituted a certain danger for the diabetic in that he believes he has done all that is necessary to maintain his health, and that he is not required to insure a proper living and proper eating by putting a curb upon his wishes. Hence, the fate of his life depends, and this is essential, not upon a month's treatment at a watering place, but upon the systematic continuance of a proper regime for the remaining eleven months of the year. It is for the best interests of the diabetic that if he wishes to maintain his health he must guard himself against an overindulgence in food that is detrimental to his well-being, even when he feels in fairly good health. He has to deny himself for the present in order that he may reap in the future. We cannot obviate this necessity in any way. The patient learns it if he is rightly instructed; and that what at first is only attained by struggle and self-denial, later on becomes second nature. The doctor who is responsible for the health and life of the patient has to fix his mind upon what the future shall bring. He must not allow himself to be influenced by the transitory likes and dislikes of the patient, but must prepare for later developments. In preparing his scheme

of treatment for this year the physician must have in view what will be the effects on the diabetic patient many years hence. If both doctor and patient keep their eyes fixed on this object, the necessary amount of restriction will appear not as a burden, but as a welcome benefit.

EXTRACARDIAC CAUSES OF FAILURE OF COMPENSATION IN VALVULAR DISEASES OF THE HEART.

By Alfred Stengel, M.D., Sc.D.,

PROFESSOR OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

The point of view of clinicians regarding cardiac pathology has always been too narrow, because they have appealed to the pathological anatomist for their data and have ignored the teachings of physiology. The solution of many questions in the pathology of the circulation lies entirely outside the domain of mere morphology and for this reason certain prevailing views of disturbances of the circulation and methods of treatment based upon such views, sadly need revision. It is a well-known fact that in cases of death following valvular disease of the heart the pathologist finds in the heart only the valvular defect and certain alterations in the myocardium and outside the heart only peripheral and visceral lesions that have resulted from passive congestion. There is nothing to indicate clearly the steps that have led from the original valvular defect to the final cardiac breakdown, nor can we hope for a solution of this important chain of events from morphological studies made after death. The intermediate stages between the valvular disease and the hopelessly dilated heart are unexplained, and seem, therefore, because so frequent, the inevitable tendency of a progressive disease. The nomenclature we use itself establishes wrong impressions leading to the same assumption of inevitable cardiac breakdown. We speak of "chronic" endocarditis, but this is a misnomer. Strictly speaking, chronic endocarditis is not a chronic disease at all in the sense that it represents a chronic and continuing process. Rather it is a result of previous acute or subacute disease, and ceases to be progressive when the damage has been done. There are undoubtedly some exceptions to this rule, as in the case of certain types of infective endocarditis and syphilitic disease of the heart; but for the most part what we recognize as chronic endocarditis or valvular disease is a deformity that has resulted from a past affection no longer active or progressive. The same thoughts apply in a lesser degree to chronic myocardial disease, though here it is probable that the process more frequently

is truly a chronic and continuous one. It is important to note that compensation is established *after* the valvular defect has been completed, and that the compensating heart is capable of maintaining its share in the work of the circulation, with some reserve power to spare, though less than the normal heart possesses. If then a lesion of a valve no longer active or progressive has been followed by satisfactory compensation with some reserve power, why does the heart fail and often before the involutional processes of age might be presumed to have weakened all organs including the heart? The clinician leaning upon the pathological anatomist, who has invariably found a degenerated and dilated heart, has concluded that this is the inevitable outcome, and misled by the inference implied in the name has accepted the result as the necessary consequence of a chronic disease. Romberg (*Krankheiten des Herzens*, second edition, p. 72) very properly states that "Hypertrophy as such does not carry with it the germs of later cardiac weakness through gradual exhaustion or the like."

The fault of the pathological anatomist and clinician alike has been that they have kept the heart itself too conspicuously before their attention, and have failed to realize that other factors outside the heart are of almost equal importance in maintaining the circulation. Placed at its centre the heart is undoubtedly the chief factor in the circulation, but without the coöperation of other agencies, mainly concerned with the regulation of peripheral circulation and with the return of the blood to the heart, cardiac power, however great, must prove unavailing. The work of the heart is expended in propelling the blood through the arterial system and arterioles into the capillary bed or through it to the veins. Here stagnation must occur if other factors did not avail to carry the stream onward through the veins. Excess of cardiac power would not be effective to drive the blood through the capillaries and into the veins under sufficient pressure to insure a return flow to the heart, for the reason that the vasomotor mechanism by contracting the arterioles interposes a resistence, and thus incidentally saves the capillaries from the injurious pressure that would break their delicate walls. The return circulation is almost wholly due to agencies outside the heart, and it is to these that the clinician must give his thought when the causes of failure of cardiac compensation are under consideration.

While it is my purpose here to emphasize the important bearing of conditions outside the heart in the eventual occurrence of failure of compensation (and if I give undue emphasis it is because this field has been neglected), it would be unfair to ignore the fact that clinicians and pathological anatomists have made clear certain conditions under which a heart the seat of valvular disease may become additionally damaged so as to become insufficient. For example, it is well known that various infections or undue physical

strains may be the occasion of rapid failure of such a heart, and long-continued strains, not immediately injurious, may gradually break down the reserve power of a heart already crippled by a valvular defect. But instead of searching industriously in all cases for some such explanation of the cardiac failure, one should review all of the factors concerned in the circulation outside as well as in the heart itself to determine if possible the cause of the overstrain. A survey of the chief agencies which participate in the circulation with some illustrations of the way in which their inadequacy may operate will serve to make clear some of the problems in the study of cardiac decompensation.

The Circulation in the Arteries. The all-important factor in maintaining a sufficient blood pressure in the arterial system and in driving the blood toward the periphery is the contraction of the left ventricle. Aided by the valve mechanisms of the heart this force drives the blood into the aorta and other large arteries under a relatively high pressure, which causes these vessels to distend. At the onset of ventricular diastole the aortic valves close and the elastic recoil of the large vessels drives the blood onward toward the arterioles and capillaries. No other propelling force operates in this field, and the maintenance of the arterial circulation, therefore, depends upon the driving power of the heart and the condition of the arterial system and the blood. In the arteries elasticity, the condition of their lining membrane, and their caliber are of importance, and the activity of the vasomotor mechanism is of particular consequence. The condition of the blood as to viscosity or bulk may be a far more potent item than we ordinarily allow. Failure of the cardiac power, and, therefore, failure of the arterial circulation, may be the direct result of progressive or intercurrent cardiac degeneration, with dilatation. Thus in cases of coronary sclerosis and thrombosis there may be a rapid failure of the ventricle, or acute myocardial disease following some infection may be the occasion of cardiac breakdown. But in the majority of cases of cardiac disease such factors are not discoverable. The explanation may in some be found in other conditions on the arterial side of the circulation. For example, a constantly recurring cause in clinical experience is arteriosclerosis. A person suffering from some cardiac disease may maintain adequate compensation until after middle life arteriosclerosis supervenes. The increased stress laid upon the heart by the inelastic vessels then occasions gradual failure until eventually the ventricle dilates and becomes wholly insufficient. Similarly, certain vasomotor conditions operating mainly upon the arterioles may be the occasion of the cardiac overstrain. Thus in renal disease the constant hypertension of the arterial system tends to exhaust a normal heart and even more speedily one already crippled by valvular disease. The bearing of the vasomotor mechanism and of conditions of the blood on

cardiac decompensation will be referred to later in somewhat greater detail.

The Circulation in the Arterioles and Capillaries. The chief factor in maintaining the flow of blood through the arterioles and capillaries is still the force of the ventricle. In the case of the capillaries certain subsidiary agencies, such as the elastic condition of surrounding tissues, the contractility of the capsules of certain organs, and muscular contractions are to be remembered; but the *vis a tergo* is doubtless chiefly responsible for the onward movement of the blood. The arterioles hold to the capillaries the relation of a buffer, which serves to protect these thin-walled vessels from the destructive pressure of the arterial system, and they at the same time operate in a protective way toward the heart through the activity of the vasomotor mechanism when undue strains threaten sudden cardiac dilatation. Their protective office toward the heart is well illustrated in aortic regurgitation, in which their dilatation reduces peripheral resistance to a minimum and relieves the heart of injurious back pressure. Studies of blood pressure in various parts of the circulation show a rapid diminution from the arteries to the capillaries. Taking as approximate estimations a pressure of 150 mm. in the aorta and the large arteries and but little less in the small peripheral arteries, 20 mm. in the capillaries, and 6 to 7 mm. in the peripheral veins, this rapid diminution in the arterioles will be evident. Formerly it was thought that much of the blood pressure was expended in overcoming resistance in the capillaries, but such figures as the above, which are approximately trustworthy, will show the contrary, as but one-tenth of the blood pressure was utilized in the capillary area. B. Lewy[1] has made calculations which seem to show that but one-fourteenth of the blood pressure is consumed in the capillaries, from which it is apparent that the chief resistance to the blood flow is in the arterioles. Campbell has pointed out that if the capillaries introduced a very considerable degree of resistance so that the pressure at the beginning would necessarily be higher than at the end their thin walls would make a funnel shape a necessary result, which is not the case.

The vasomotor mechanism is mainly operative upon the arterioles and through the contraction or dilation of these vessels regulates blood pressure as a whole and the distribution of the blood in different organs. The integrity of the whole mechanism is dependent not only upon the normality of the arterioles and the nerve centres and fibers that make up the vasomotor system, but also, and perhaps in specially important ways, upon various internal secretions or products of tissue metabolism. Organic change in the arterioles is probably always associated with change in the larger arteries

[1] Quoted by Tigerstedt.

and the influence of such changes on the work and eventually on the preservation of the heart is commonly recognized. Changes in the nervous mechanism are little known except such as accompany certain organic diseases of the central nervous system and acute infections, as well as certain so-called neuroses. A much larger group of conditions as yet but imperfectly known is that in which the internal secretions or metabolic processes suffer derangement to the detriment of normal vasomotor conditions. The high pressure of nephritis and the low pressure of Addison's disease may be cited as extremes, but there is probably a large number of less conspicuously active conditions in which vasomotor disturbances play an important role. It is impossible at the present time to specify the directions in-which various nutritional disorders operate, but it is safe to assert as a generalization that a number of diseases or conditions attended with nutritional or metabolic disorders act injuriously upon the vasomotor system and eventually serve to overtax cardiac power. We may therefore in many cases seek in this direction for an explanation of the final overthrow of a heart in which valvular disease has existed.

The splanchnic circulation is of special interest in connection with the whole vasomotor mechanism, as it is by far the largest vascular field in the body and the one most immediately involved in vasomotor influences. Closely connected with its peculiar responsiveness to vasomotor control is its constantly recurring activity in the processes of digestion. One need but recall the enormous repletion of the mesenteric and intestinal vessels in an animal killed while the intestinal canal is overfull and the relatively ischemic conditions in the fasting animal to gain an impression of the possible bearings of habitual overfeeding as contrasted with moderation. Recent investigators have sufficiently proved the influence of sclerosis of the mesenteric vessels in determining systemic hypertension, but doubtless long before such organic changes have taken place in the bloodvessels, recurring or continuous taxations upon the splanchnic mechanism may influence injuriously the circulation as a whole. Not only conditions of hypertension but repletion of the abdominal circulation may act injuriously, as is shown by the fact that rabbits may be killed by holding them upright and thus causing overfilling of the vessels of the splanchnic area.

Clinical experience abundantly confirms the results of experimental investigation in showing how greatly continued overdistention of the splanchnic circulation taxes the whole circulation and eventually the heart. One of the commonest types of anginoid conditions of the heart is that which occurs in overfed men with large and perhaps somewhat pendulous abdomens. In such individuals, circulatory disorders are often encountered after middle life when previously every indication of robust health had existed.

After the age of fifty to fifty-five years, evidences of cardiac weakness may make their appearance—impure heart sounds, a systolic mitral murmur, signs of dilatation, undue dyspnea on slight exertion, mild anginal pains, and eventually cardiac failure. The explanation of these symptoms may be found in myocardial disease which has resulted from long-continued overfeeding and disturbance of normal metabolism, but probably in a more direct way impediments in the splanchnic circulation have affected injuriously the general circulation and the cardiac power. The beneficial effect of abdominal support and of careful regulation in diet in such cases is a suggestive evidence that the difficulty is more largely a matter involving the mechanical conditions of the abdominal circulation and perhaps its vasomotor mechanism than one occasioned by preëxisting myocardial disease. Finally, however, if conditions are not improved actual dilatation of the cardiac chambers results, and it is not often easy to determine whether a toxic weakening of the heart muscle or some extracardiac disturbance of the circulation has been mainly at fault.

The Venous Circulation. On the venous side of the circulation the important factors are: (1) Muscular contractions, (2) the valves in the veins, (3) the normal tissue tone, (4) the aspirating effect of the movements of the chest, and (5) gravity.

Muscular contractions are of prime importance in forcing the blood through the veins toward the heart. The value of this factor in the circulation is evident when one recalls the increased flow of blood from a severed vein of the arm upon voluntary contractions of the muscles of the forearm and hand in opening and clenching the fist. Less demonstrably but none the less certainly the effect of athletic exercise upon the circulation illustrates the influence of muscular contractions in furthering peripheral circulation. On the contrary, one sees in those who are habitually sedentary the evil effects resulting from a lack of muscular contractions, and especially in those whose occupations requires much standing without muscular exertions to change position or in convalescents whose weakness prohibits active use of the lower extremities. In these conditions (in which doubtless vasomotor conditions also play a part) there is a tendency to venous stasis which gradually operates in the direction of overtaxing the heart, partly by introducing an obstruction in front of the arterial circulation and partly by depriving the heart of an adequate return flow.

Another effect of muscular exertion is quite apart from the direct effort in compressing the veins and forcing the blood toward the heart. This is the suction action which the stretching and increase of capacity of the veins occasion when certain sorts of muscular effort are employed. When the arms are widely extended and the body is thrown back there is an appreciable increase in the capacity of the large veins and a tendency to draw the blood

toward the heart. This explains to some extent at least the desire of persons who have been for some time in a cramped position to stand and extend the arms.

The effect of the venous stasis that results from lack of muscular contractions in such conditions as sedentary life, standing occupations, prolonged weakness after illness, and paralysis of the extremities is at first confined to the venous side of the circulation and is manifested by coldness, lividity, and edema of the extremities. Eventually, however, if such venous stasis is extensive the heart itself and the arterial side of the circulation must suffer because, as before stated, an adequate return supply of blood to the heart is wanting and on the other hand the resistance in front of the capillaries to some extent retards the arterial flow. Such impediments to the peripheral circulation unless very extensive can have little effect upon a normal heart, but can more readily injure one that is already weakened by a valvular lesion.

The effect of deficiency in the muscular contractions—thoracic, diaphragmatic, and abdominal—concerned in respiration has a somewhat different explanation from that applying to the peripheral muscular system and will, therefore, be considered separately.

The valves of the veins are an important adjuvant to muscular action in directing the return circulation of the blood. One sees the immediate results of their insufficiency in the extreme venous repletion that occurs in cases of phlebectasis. Thus in women who have extensive varicosity of the veins of the legs after repeated childbirths a large part of the blood of the body may be stagnated in the lower extremities and cardiac weakness, palpitations, faintness, vertigo, and other symptoms of circulatory derangement may result. These symptoms may be controlled by narrowing the venous bed by the application of elastic bandages.

Tissue tone is an indefinite, though doubtless real, condition which may be of considerable importance in regulating peripheral circulation. Its absence is more demonstrable than its presence, as, for example, when the relaxed conditions of paralysis or following protracted illness determine stasis of the peripheral circulation and edema. Compared, however, with muscular activity this factor is of little importance in the return circulation, and its absence plays no conspicuous part in determining circulatory derangements.

The aspirating effect of movements of the thorax in respiration is a factor of prime importance in the venous circulation. During ordinary respiration the pressure in the large intrathoracic veins is approximately 6 mm. of mercury; during forced inspiration it may be depressed to 20 mm. The effect of such reduction of the central venous pressure must be obvious. On the contrary, conditions such as emphysema of the lungs, intrathoracic effusions, tumors, etc., in which thoracic expansion is interfered with, occa-

sion marked peripheral congestion by reducing the aspiratory influence of free movements of the chest.

The act of respiration is also of assistance in the return circulation of the blood in another way. The contractions of the abdominal muscles and of the diaphragm by compressing the abdominal viscera tend to expel the blood from the abdominal circulation and force it toward the heart.

Clinical observation abundantly illustrates the beneficial effects of respiration in maintaining proper circulation, and even more clearly demonstrates the unfavorable effects of conditions in which the respiratory movements are deficient. Not only does one see this in the well-known effects of emphysema of the lungs, pleural effusions, tumors, aneurysms, and other intrathoracic diseases, but also in the circulatory weakness that results from abdominal obesity, enteroptosis, and other abdominal conditions which interfere with the normal activity of the diaphragm and abdominal muscles. Abdominal fatness in particular is of clinical importance, and seems after middle life to be the frequent cause of failing cardiac power. In such cases one must recognize several operative factors, such as the influence of disturbed vasomotor conditions, of gravity, and perhaps of associated fatty deposition in and about the heart; but in addition to these, the effect of decreased respiratory activity must be considered. A significant proof of this is manifest in the improvement obtained in such cases by systematic respiratory exercises.

Gravity is an aid to the circulation only in the case of that of the head, where, it may be observed, muscular contractions play less of a part in assisting the return circulation than in the extremities and trunk. It is a force that needs to be overcome by other factors in the abdomen and limbs, and under certain circumstances becomes a considerable obstacle to the return flow of blood. Thus in occupations requiring prolonged standing there is a pronounced tendency to stasis in the legs, and doubtless in elderly individuals with pendulous abdomens the same influence affects the abdominal circulation injuriously as it does in animals held in an upright position. In persons convalescent from acute diseases one frequently finds that this cause together with vasomotor weakness, muscular atony, and loss of tissue tone determine the occurrence of edema of the feet. Eventually such peripheral stagnation has an unfavorable effect upon the heart and the arterial side of the circulation.

The Effect of Quality and Mass of Blood on the Circulation. The viscosity of the blood is manifestly of importance in the determination of the work of the heart, but we lack precise data to estimate this factor properly. Such facts as are available indicate that excessive eating and especially excessive meat eating, as well as faulty renal elimination, tend to increase the viscosity of the

blood and thereby increase the work of the heart. How much the condition is responsible for the circulatory difficulties of overfed and overfat individuals as contrasted with the effects of impaired muscular activity, of reduced respiratory activity and of gravity must be a matter of some uncertainty. The rather immediate effect of overfeeding, without injurious overdistention of the stomach, that is observable in some cases of cardiac weakness would suggest that the conditions of the blood resulting therefrom may be of material consequence. A medical man, himself a considerable student of cardiovascular troubles, informs me that he has invariably suffered attacks of acute pulmonary edema and cardiac asthma after meals rich in protein, and that by care to avoid such a dietary he has been able to avoid their occurrence. This may of course be explained on other grounds, but is at least suggestive in the direction of possible modification of viscosity of the blood.

Increased quantity of blood or plethora vera is a condition which clinical observation as well as experimental investigation have shown to be at the most of brief duration. The introduction of excessive amounts of fluid either through the gastro-intestinal tract or into the veins is speedily followed by vasodilatation, exudation, and glandular activity which restore the normal pressure of the vascular system. Though a permanent plethora vera does not occur, a temporary overfilling of vessels may result from excessive ingestion of fluid, and clinically, as well as experimentally, dilatation of the heart has been observed, and some cases of sudden death have probably resulted from this condition. Often no doubt persons affected with some form of cardiac weakness suffer from repeated strains due to temporary overfilling of the vessels as a result of excessive drinking of water or other liquids. Oertel long ago pointed out the unfavorable result of a too liberal ingestion of fluids by persons suffering from cardiac weakness, and an abundance of clinical observation confirms his views in this particular.

The Conservative Relations of the Liver and Spleen to the General Circulation. The capacity of the liver and spleen for blood is considerable and clinical, as well as experimental, evidence in abundance shows that these organs are capable of enormous vascular distention at times when the overfilling of the vascular system threatens cardiac dilatation. Experiments to determine the degree of acute plethora that may be sustained without injurious consequence by intravenous injection of salt solution show that the liver undergoes enormous enlargement before any signs of dilatation of the heart become manifest. Clinically it is well known that the liver enlarges and contracts in cases of cardiac disease in proportion as cardiac compensation is maintained or deficient, while the general circulation shows no commensurate

fluctuation in venous repletion. The conclusion from such observations must be that the liver acts in a measure as a safety reservoir to protect the right heart against overfilling.

The spleen as a subsidiary of the portal circulation aids in the same direction. In the later stages of chronic cardiac disease when secondary induration of the liver has occurred, and distention becomes difficult or impossible, the protective influence of the liver is lost and cardiac dilatation soon occurs.

Having reviewed in this rather brief and undetailed manner a variety of extracardiac adjuvants of the circulation, it is proper to conclude that there are many directions in which one must seek for the occasion of cardiac overstrain when a heart previously damaged by endocardial disease begins to fail in its compensation. The tendency to which I alluded in the beginning of my remarks, and which is largely attributable to the dominating influence of pathological anatomy in our clinical deductions, has been to regard the heart as somehow foredoomed to failure in such cases. My own clinical experience, however, in conjunction with a consideration of the physiological data I have here sketched in outline have led me to believe that the causes of final cardiac failure are usually quite outside the heart itself. Lack of regulated exercise, habits of overeating, obesity, disturbances of the abdominal circulation, improper breathing or thoracic diseases, and conditions of the blood are among these extracardiac conditions that may be of importance. I have alluded to the possibility that metabolic disorders may play some part by exercising an unfavorable influence on the vasomotor system or on the viscosity of the blood, but do not dwell upon these because the data are not sufficient to justify more than a hint at the importance of such conditions. It would have been proper to enlarge upon the effect of advancing arteriosclerosis and its attendant hypertension in determining cardiac breakdown in cases of old valvular disease, but this is a fact so well recognized that I have ignored it in order to keep other and less frequently considered conditions more prominently n mind.

What I have been attempting to bring forward must not be thought to have merely an academic interest. It is an intensely practical matter for the physician who has to deal with cardiac disease from the time of its inception to the final termination. He has been properly advised to avoid medication during the stage of compensation, and has in a general way been instructed to pay particular attention to the hygienic regulation of the patient's life; but he has had little guidance regarding exact details based upon a recognition of the probable causes of subsequent cardiac failure. Physician and layman alike have been aware that physical or nervous strains, exhausting occupations, lack of proper sleep, and similar conditions are injurious because they tend to exhaust

cardiac power, and the pathologist has shown how intercurrent infectious diseases may operate unfavorably by causing myocardial complications, but aside from such knowledge, there has been little to guide the practitioner in the management of compensated cases of cardiac disease. The too one-sided view of the problem and one concerned only with upholding the myocardial efficiency has indeed led to certain decidedly disadvantageous methods of treatment. For example, the desire to avoid physical strain has occasioned a common practice of denying all exercise to persons with compensated lesions. In view of what has been before stated, this tends to retard the proper return circulation and to bring about all the unfavorable effects of sedentary life. Moderate and well-regulated exercise is, on the contrary, of the greatest advantage during the stage of compensation, and even after the reserve power is beginning to be deficient. In the matter of diet, also, the overemphasis placed upon the integrity of the heart muscle has sometimes occasioned erroneous practice. In the effort to keep the heart well nourished and perhaps establish better compensation, a liberal and often excessive dietary has been advised, and doubtless unfavorable results have often resulted Finally, when compensation has begun to fail, the monopoly of responsibility has been laid upon the heart itself, and no other course suggested than to resort to stimulants or general and cardiac tonics. Fortunately there has been some improvement in the management of circulatory disorders in recent years, thanks to the labors of those who have busied themselves with mechanical, physical, and hydrotherapeutic measures; but the possible usefulness of these agencies has been so generally associated in the mind of physicians with certain health resorts that far too little effort has been made at home treatment along the same lines. In the last analysis it will be found that even at this day practically all cases of beginning cardiac decompensation are relegated to purely medicinal treatment. Not even the excellent scientific investigations of the last decade with new and refined instrumental methods of study have availed to correct matters, for here again the heart itself has been mainly the object of study, and but little attention has been given to the practical bearings of the peripheral circulation. I have not had the purpose, even remotely in mind, to undervalue the importance of the heart itself, but rather to point out that the circulation must not be looked upon as a system of tubes through which the blood is bound to flow smoothly so long as the central driving force remains intact. Nothing could be farther from the truth. If it were true we would be justified in bending every effort to the maintenance of the cardiac power without regard to the rest of the circulation. As it is not so, the physician will do well to consult the physiologist to learn in what manner the whole circulatory system is regulated, and how it compensates for imperfections

in one place or another. The conclusions that necessarily follow such an inquiry are the occasion for the discussion I have presented.

THE KINETIC THEORY OF GRAVES' DISEASE.

By GEORGE W. CRILE, M.D.,

PROFESSOR OF SURGERY IN THE WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO.

LET us first point out some of the shortcomings of the leading hypotheses held at present—namely, the auto-intoxication, the infections, the nervous, and the thyroid hypotheses. The auto-intoxication and the infection hypotheses do not explain why cretins do not have Graves' disease, and why the disease so frequently follows in the wake of some strong emotional excitation and is engrafted on colloid goitre, benign tumors, and even cancers of the thyroid gland; nor do they explain those cases caused by excessive dosage of thyroid extract or of iodine, nor the relation of Graves' disease to adolescence or to pregnancy. The infection and the auto-intoxication theories are not at present widely held, and their basis seems insecure.

The two hypotheses that have the strongest support at present are the nervous origin and the thyroid origin. The theory that the disease is primarily in the nervous system scarcely explains the cases whose origin lies in excessive doses of thyroid extract, nor the cures wrought by excision of a lobe, or ligation of the poles of the thyroid, nor does it explain the constant presence of hyperplasia of the thyroid.

Those who believe that Graves' disease is a disease of the thyroid gland alone, and may be regarded as a hyperthyroidism, must, on the other hand, be at a loss to explain the frequent cure by physiological rest and the relapses that may occur after an apparently sufficient amount of the gland is removed if the patient is again submerged in the environment that originally produced the disease. If Graves' disease is simply a thyroid problem, then if the operation has removed a sufficient amount of gland there should follow at once a cure just as definite as the symptoms of hyperthyroidism due to overthyroid feeding are relieved on withholding the thyroid extract. This, of course, does not follow. It is difficult to understand how the thyroid hypothesis accounts for the cases induced by nervous strain, and how it accounts for the cases in which the administration of thyroid extract in colloid goitre causes the disease, because usually the effect of thyroid extract and of iodine is to diminish the activity of the thyroid —as seen in the disappearance of goitre in adolescent girls.

These two hypotheses harmonize many of the facts, but apparently neither is adequate; but the true hypothesis must surely account for the lesions of both the nervous system and of the thyroid gland. But in its gross pathology there is practical agreement. Lesions are found in cells of all parts of the cerebrum, the cerebellum, to a less degree of the medulla, and little or not at all in the spinal cord. The heart, voluntary muscles, the thyroid, the adrenals, the pancreas, the liver, the lymphatics, the thymus, the spleen, the lymphatic glands, the skeletal muscles, the skin, the bony skeleton, the teeth, the hair all show pathological modifications of varying degrees according to the duration and the severity of the disease. *Nearly all of these structural changes may be produced by the emotions.* The significance of this will be later seen. From the foregoing it is obvious that whatever the cause it is a malady of protean manifestations.

Diseases are assigned to classes they most resemble. Does exophthalmic goitre closely resemble any disease? I know of none. Does it resemble so closely that it might be related to any normal process? Clinicians have always remarked upon its resemblance to the emotions, especially that of fear and the exhaustion of overexertion. We will first compare the phenomena of Graves' disease and those of fear and worry.

The following phenomena of worry, nerve strain, and fear are nearly identical with the phenomena of Graves' disease—namely, increased heart beat, increased and altered respiration, rising temperature, sweating, muscular tremors, protruding eyes, loss in weight. Cannon has found an increased amount of adrenalin in the blood in fear; in each there is increased blood pressure; muscular weakness; digestive disturbances; falling out of the hair; decay of the teeth; skin eruptions; disturbance of the growth and change in texture of the nails; impaired nervous control; hypersusceptibility to stimuli; lack of initiative, and decreased mentality. In protracted intense fear the brain cells show marked physical changes. In Graves' disease analogous changes are seen. Disregarding the thyroid and the exophthalmos, if the symptoms of acute fear continued for weeks and months, who could differentiate between Graves' disease and fear?

Surely the phenomena of Graves' disease and those of the emotions present a striking resemblance even in their minor details. The first question that arises is what is the origin of the emotions? What is the purpose of their phenomena and may Graves' disease and the emotions have a common origin? The former represent a normal process and the latter a pathologic.

It may be assumed that the same principles underlie the emotions of fear and of anger and of sexual love.

I shall limit my discussion mainly to the strongest emotion, *fear.* I believe that it can be shown that the emotion of fear can

be elicited only in animals that utilize a motor mechanism in defence against danger or in escape from it. The defence of the skunk is a diabolic odor which repels its gross enemies. The skunk has no adequate equipment for defence or escape by muscular exertion. The skunk has little or no fear. Certain species of snakes are protected by venom. They possess no other adequate means of defence or escape. They show no fear. Animals having mechanical protection, as the turtle and porcupine, have little fear. Other animals because of their prowess have but few fears. The lion, the grizzly bear, the elephant are examples. It is obvious that fear is not universal. The emotion of fear, as I believe, is felt only in those animals whose self-preservation is dependent upon the uncertain adequacy of their power of muscular exertion, either in defence or in flight.

What are the principal phenomena of fear? They are palpitation of the heart; acceleration of the rate and alteration of the rhythm of the respiration; cold sweat; rise in body temperature; tremor; pallor; erection of the hair; increase of certain internal secretions; suspension of the principal functions of digestion; muscular tremors; protrusion of the eyes; the function of the brain is wholly suspended, except that which relates to the self-protective response to the object feared. Neither the brain nor any other organ of the body can respond to any other lesser stimulus during the dominance of fear.

From the foregoing it would appear that under the influence of fear, most, perhaps all, of the organs of the body are divided sharply into two classes: (1) Those that are stimulated, and (2) those that are inhibited. Those that are stimulated are the entire muscular system; the vasomotor and locomotor systems; the senses of perception; the respiration; the mechanism for erecting the hair; the sweat glands; the thyroid gland; the adrenal gland (Cannon); the special senses. On the other hand, the digestive and procreative functions are inhibited. What is the significance of this grouping? So far as we know the organs stimulated increase the efficiency of the animal for flight or for fight. It is through skeletal muscles that the physical attack or escape is effected; these muscles alone energize the claws, the teeth, the hoofs, and the means for fight or flight. The increased action of the muscles of the heart and the bloodvessels increases the efficiency of the circulation; the secretion of the adrenal gland causes a rise in the blood pressure; the increased action of the thyroid gland causes an increased metabolic activity; there is evidence that glycogen is actively called out, it being the most immediately available substance for the production of energy; the increased activity of the respiration is needed to supply the greater requirements of oxygen and the elimination of the increased amount of waste products; and regulation of heat supplying the increased

activity of the sweat glands is needed to regulate the rising temperature of the body due to the increased metabolism. The activity of all of the organs of perception—sight, hearing, smell—is heightened for the purpose of perceiving the more accurately the danger. It could not be a mere coincidence that the organs and the tissues that are stimulated in the emotion of fear are precisely those that are actually utilized in the perception of danger and in a physical struggle for self-preservation. Among the organs inhibited are those that have mainly to do with digestion and procreation, and the muscles that are not concerned in a physical defence or escape.

Are there any other organs stimulated by fear except those that can or that do assist in making a defensive struggle? I know of none. On the other hand, if an animal could dispense with his bulky digestive and other organs, whose functions are suspended by fear—if he could, so to speak, clear his decks for battle—it would be advantageous. Although the marvelous versatility of natural selection apparently could devise no means of affording this advantage, it did the next best thing—it turned off the nerve current and saved the vital force these non-combatants ordinarily consume in the performance of their functions. Whatever the origin of fear is, its phenomena are due to a stimulation of all of the organs and tissues that add to the efficiency of the physical struggle for self-preservation through the motor mechanism and an inhibition of the functions of the leading organs that do not participate—the non-combatants, so to speak. Fear arose from injury. By the slow process of a vast empiricism nature evolved the wonderful defensive motor mechanism of many animals and of man. Now the stimulation of this mechanism leading to a physical struggle is action; and the stimulation of this mechanism without action is emotion.

We may say then that fear is a *phylogenetic fight* or *flight*. On this hypothesis all of the organs and parts of the entire animal are integrated, connected up, or correlated, so that the motor mechanism may play its maximum role in self-preservation. Man fears not in his heart alone, not in his brain alone, not in his viscera alone, but he fears in every organ and tissue of his body; each organ or tissue apparently is stimulated or inhibited according to its help or hindrance in the physical struggle for existence. In thus playing all or most of the nerve force on the nerve-muscular mechanism for defence alone a greater physical power is developed, hence, it is that animals or men under the stimulus of fear may be able to perform preternatural feats of strength. Then, too, for the same reason the exhaustion following fear will be the greater, as the powerful stimulus of fear drains the cup of nervous energy, though no visible action may result. An animal under the stimulus of fear may be likened to an auto-

mobile with the clutch thrown out, but whose engine is racing at top speed. The gasoline is being consumed, the complex machinery is being worn out, but the machine as a whole, does not move, though the power of its engine may cause it to tremble. In applying this conception to human beings today it must be borne in mind that man has not been presented with any new organs to meet the requirements of the present state of civilization; indeed, not only does he possess the same type of organs as his savage fellows, but also the same type of organs possessed by the lower animals. In fact, the present work of civilization of man is now operated with the primary equipment of brutish organs. Contrasted with the entire duration of organic evolution, man has come down from his arboreal abode and resumed his new role of increased domination over the physical world but a moment ago. And now sitting at his desk in command of complicated machinery of civilization, when, for example, he fears a business crash, it is in the terms of his ancestral physical battle in the struggle for existence. He cannot fear intellectually, he cannot fear dispassionately; he fears with all his organs, and the same organs are stimulated and the same organs are inhibited as if instead of being a battle of credits, or position, or honor it were a physical battle with teeth and claws. Whether the cause of acute fear is moral, financial, social, or stage fright, the heart beats wildly, the respiration are accelerated, perspiration is increased, and there is pallor, trembling, indigestion, and so forth. The phenomena are those of physical exertions for self-defence or escape. There is not one group of phenomena which expresses the acute fear of the trusted official who suddenly and unexpectedly faces the naked probability of the penitentiary; another for a patient who unexpectedly finds he has a cancer; or for the hunter when he shoots his first big game; or for the passenger in a railway wreck; or the animal in the wilds confronting a formidable enemy. Nature has but one means of response, and whatever the cause, the phenomena are always the same—always physical. All forms of fear as it seems to me express themselves in similar terms of ancestral contests, and on this law dominate the various organs and parts of the body. Anger and fear express opposite states. Fear expresses the evidence of a strong desire to escape from danger; anger a strong desire to physically attack and vanquish opposition. This hypothesis is strongly supported by the outward expression of fear and anger. Animals with no weapons for attack show no anger; animals that have no means of self-defence by muscular action show no fear. When a man in ordinary vocation is conducting a struggle for existence against his rivals, and when the contest is at its height, he may clench his fists, pound the table, perhaps show his teeth, and he may exhibit every expression of physical combat. Fixing the jaw and showing the teeth in anger merely

emphasize the remarkable tenacity of phylogeny. Although the development of the wonderful efficiency of the hands has led to a modification of the once powerful canines of our progenitors, the ancestral use of the teeth for attack and defence is still attested in the display of anger. In all stations of life difference of opinion may lead to argument, and argument to physical combat—even to the point of killing.

Physical violence of the savage and the brute still lies surprisingly near the surface. Although there is not convincing proof, still there is strong evidence that the effect of the stimulus of fear upon the body without physical activity is more injurious than the effect of fear with physical activity. It is well known that the soldier lying under fire awaiting in vain for orders to charge suffers more than the soldier that flings himself into the fray; that a wild animal in an open chase against capture suffers less than when cowering in captivity.

Civilized man may be said to be in a state of autocaptivity. The child has no desire to conform to the conventions of his elders, on the contrary, he naturally prefers to wear no clothes, to climb, to run, and play, and be dirty—to fight and hide and hunt and fish and kill according to the primitive design of his mind and body by his evolution through lower forms of life. It is such a commonplace that we scarcely realize the immense significance of the difficulty of the training of our children. For some twenty years the mother, the father, brothers, and sisters, friends, teachers, the community at large—even the policemen—are engaged in the difficult task of training and taming a child to the conventions and the work of his adult life. Even after this long period of taming and training this natural savage may in the end break out in many savage ways. The wild animals and primitive man have but little difficulty in bringing up their young in the ways designed for them by nature, but each generation of man must spend a prodigious amount of time in training its young for the obligations and duties of civilized life, then in time they do the same for the generations to follow—in other words, man exists in a state of autocaptivity, and this is a fact of great importance. In civilized life there is much restraint, little action, much emotion. An unexpressed slumbering emotion is measurably relieved by action. It is probable that the various energizing substances needful in physical combat such as the secretions of the thyroid, the adrenals, glycogen, etc., but which are not consumed in action may, if frequently repeated, cause physical injury to the body. That the brain is definitely influenced, even damaged by fear, has been proved by the following experiments:

Rabbits were frightened but not injured, and not chased by a dog. After various periods of time the animals were killed and their brain cells compared with the normal. Widespread changes

were seen. The principal gross phenomena expressed by the rabbit were rapid heart, accelerated respiration, prostration, tremors, and a rise in temperature.

The dog showed similar phenomena, excepting instead of muscular relaxation, as in the rabbit, it showed aggressive muscular action. Both the dog and the rabbit were exhausted, and although the dog exerted himself actively and rabbit remained physically passive, the rabbit was much more exhausted than the dog.

Other observations were made upon the brains of foxes chased for various distances by members of a hunt club, then finally overtaken by the hounds and killed. The brain cells of these foxes as compared with those of a normal fox showed extensive physical changes.

Man is capable of only such actions as his ancestors have through evolution—that is, phylogeny—made possible, and only by association. When an individual experiences such a contact with his environment that in his phylogeny would have led to action, but in him no physical action ensues, though there is widespread stimulation in preparation for action, this is emotion.

The effect of repeated stimulations of the emotions is seen in the destructive phenomena of worry, of fear, and, in a lesser degree, though analogous in principle, the phenomena of sexual love. In the case of a young woman with indigestion, insomnia, low spirits, loss of weight, and general loss of vitality and interest, who would venture to assert, in the absence of a correct history, of which she was the victim, some disease or a disappointment in love? Now in the history of cases of Graves' disease there is again and again given voluntarily or as an admission an account of some strong emotional stimulant—some deeply disturbing fact which thrusts itself upon the consciousness instantly on awakening—rather it awakens its victim in the course of the night and in the early morning; some dominating emotional stimulant which absorbs the attention during the day and disturbs the sleep in the night; the ever-recurrence of this evil stimulus is attended by an increase of all the emotional phenomena, so that gradually, indeed imperceptibly, the stimulus remains constant; the eyes protrude; the thyroid is enlarged, and full-blown Graves' disease is seen, a disease primarily involving the entire motor mechanism, or emotional mechanism.

The following is typical: A broker up to the panic of 1907 was in his usual health. During this panic his fortune and that of others was for almost a year in jeopardy, finally ending in failure. During this heavy strain he became increasingly more nervous, and imperceptibly there appeared a pulsating enlargement of the thyroid gland; an increased prominence of the eyes; marked increase in perspiration, even profuse sweating; palpitation of the heart; increased respiration, with frequent sighing; increase in

blood pressure; there was tremor of many muscles; rapid loss of weight and strength; frequent gastro-intestinal disturbances; loss of normal control of his emotions, and marked impairment of his mental faculties. He was as completely broken in health as in fortune.

These phenomena resemble closely those of fear and follow in the wake of a fear strain. In young women this disease often follows in the wake of disappointment in love; in women, too, it frequently follows in the wake of an illness of a child or parent in which the double strain of worry and of constant care are present. Since such strains usually fall heaviest upon women, they are the most frequent victims. In adolescent girls, when the innumerable stimuli due to the development of the sexual functions fall upon the thyroid and other glands, there is frequently observed an enlargement of the thyroid. Either iodine or thyroid extract in moderate doses will cause shrinkage of such a gland; but if these subjects in addition to their phylogenetic stimuli are subjected to unusual environmental stimuli, Graves' disease may develop.

Whatever the exciting cause of exophthalmic goitre, whether unusual business worry, disappointment in love, a tragedy, a strong fear, the illness of a loved one, an acute infection, overdose of iodine or thyroid extract, or of unknown cause, the symptoms are alike and closely resemble the phenomena of one of the great primitive emotions. Now, how could disappointment in love play a role in the causation of Graves' disease? If the hypothesis presented for the explanation of the genesis and the phenomena of fear is correct then it would hold for the emotion of sexual love. If fear is a phylogenetic physical defence or escape, but without resulting muscular action, then love is a phylogenetic conjugation without physical action. The quickened pulse, the leaping heart, the accelerated respiration, the sighing, the glowing eye, the crimson cheek, and many other phenomena are merely phylogenetic recapitulations of ancestral acts.

The thyroid gland is believed to participate in such physical activities, hence, it could well follow that many organs, including the thyroid gland of the disappointed maiden who is intensely integrated for a youth, will at every thought of him be subjected to a stimulation analogous to that which attended the ancestral consummation and under certain conditions it may inaugurate Graves' disease. Now, a happy marriage has many times been followed by a cure of the exophthalmic goitre which appeared in the wake of such an experience. The victims of Graves' disease present a counterpart of emotional exhaustion. The emotions in Graves' disease are abnormally powerful, as illustrated by personal observations of death from fear alone in several victims of this disease. Whatever the cause of this disease of the motor mechanism or the emotions the symptoms of Graves' disease are

the same; just as in fear, the phenomena are the same whatever the cause. In Graves' disease there seems to be a composite picture of an intense expression of the great primitive emotions. If Graves' disease is a disease of the motor mechanism or of the emotions, what is the source of the constant flow of stimulation that continues the disease? A stimulation that may be constantly present in waking and in sleep for months and years. The stimulus could scarcely be of nervous origin caused by environment alone, because the stimulus has a more even flow than environmental contact alone could possibly have. The following facts suggest that the thyroid gland plays the leading role of secondary stimulation: In suitable cases of Graves' disease if the activity of the thyroid gland is sufficiently decreased the phenomena of the disease are immediately diminished, and in favorable cases the patient is restored to approximately the normal condition. The heart slows, the respiration falls, the restlessness diminishes, digestive disturbances disappear, tremors decrease, there is a rapid increase in the body weight, and the patient gradually resumes his normal state. On the other hand, if to a normal individual extract of the thyroid gland is administered in excessive dosage over a period of time, there will develop nervousness, palpitation of the heart, sweatings, loss of weight, slight protrusion of the eyes, indigestion—in short, there will be produced, artificially, most of the phenomena of Graves' disease and of the strong emotions. On withholding the thyroid extract these phenomena may disappear. I use the qualifying word "may," because I have seen a number of cases of excessive administration of thyroid extract end in real Graves' disease. On the other hand, when there is too little or no thyroid gland the individual becomes dull and stupid and emotionless, though he may be irritable. This does not refer to those cases of hybrid myxedema due to a combination of the wreckage of Graves' disease and thyroid deficiency. The motor mechanism here is burned out.

Hence, we see that the phenomena of the emotions may be, within certain limits, increased, or may be diminished, or abolished by increasing, diminishing, or totally removing the thyroid secretion. Graves' disease may be increased by giving thyroid extract and by any of the excitants of the emotions. It may be diminished by removing a part of the gland or by partially interrupting its nerve or its blood supply, or by physiological rest. Finally, in Graves' disease there is at some stage an increase in the size and in the number of the secreting cells of the thyroid gland.

The phylogenetic identity of physical injury and fear tells us why psychic shock is identical with traumatic shock; why in cases of exophthalmic goitre the psychic stimuli increase the phenomena of Graves' disease precisely the same as physical stimuli. Why the fear of operation causes the same exacerbation of all the symptoms as the physical injury of tissue in the course of

operation. Both physical injury and psychic stimuli cause a self-protective response which causes a stimulation of the motor or emotional mechanism. In Graves' disease, this mechanism being highly sensitized, the effect of either physical or psychic stimuli is immensely increased; hence, the startling effect of operation often seen. In Graves' disease there seems to be established a pathological stimulation of the entire motor mechanism of the human body. Its phenomena resemble continuous motion or at least a continuous primary stimulation of the entire motor mechanism. The nervous system alone is capable of initiating such a motor excitation, but as we have seen its continuation is effected through the agency of secondary influence—that of the activating ductless glands—especially the thyroid, which is the only gland whose secretion, wholly independent of the inauguration by the nervous system, is capable of equally stimulating the entire motor mechanism and of producing identical phenomena. By motor mechanism is meant the entire complicated machinery used in the production of physical action. The role of the thyroid is that of an activator. But the action of the thyroid, like the action of all the other organs of the body, is inaugurated either directly or indirectly by the nervous system. Environment, as Sherrington has said, drives the nervous system and the nervous system drives the entire organs of the body.

The question which next confronts us in a given case is this: What has caused the inauguration of the thyroid activity and what impels its continuation? Let us consider some of the conditions present and which seems to serve as exciting causes: It may follow an acute infection such as tonsillitis, or in the wake of an infectious disease, as measles, typhoid, etc.; it may follow large doses of iodine; administration of excessive dose of thyroid extract, especially if there is present a colloid goitre; overwork, especially in adolescence; worry; phychic shock and emotional disturbances. All these exciting causes produce a lowering of the threshold of the nervous system to stimuli and a diminution of the normal control of the brain. This statement is based on the clinical observation of hyperexcitability and the demonstration of actual lesions of the brain cells in each of the above-mentioned exciting causes; when the threshold is lowered, environmental stimuli will produce an increased activation of the brain, which in turn will drive to greater activity the various organs of the body, including the thyroid.

The impairment of nervous control by various diseases and nerve strain would expose the thyroid gland to abnormal stimulation. This stimulation in turn would increase the output of the activating thyroid secretion, the effect of which would be to further increase the excitability of the brain, or, in other words, would sensitize the brain. This reciprocal interaction may continue

until Graves' disease is evolved. The precise means by which this interaction is continued, that is, the physical chemical process by which it is wrought—is unknown, but it is known that this pathological interaction may be broken at either end—namely, by restoring to the brain its power of normal control, or by diminishing the output of thyroid secretions. If a case of Graves' disease can be so managed as to secure sufficient rest, secure a sufficient reduction of environmental stimuli, the disease may be arrested or cured. It is usually impossible to promptly enough disentangle this explosive vicious circle, and frequently the mere effort at cure becomes an exciting cause. If the brain could enter into the state of actual hibernation, like a bear, the disease would certainly be cured; but unhappily the knowledge of the gravity of the disease itself becomes one of the psychic excitants which aggravates the disease, the entanglement becomes frequently hopeless, and, like the Gordian knot, it must be cut. Although a widening experience confirms the value of surgical treatment of Graves' disease, there are still some who are not yet prepared to admit it.

Perhaps the strongest point of objection raised by those who oppose the phylogenetic hypothesis is that of admitting the benefits which follow surgery. While admitting the benefits of surgery they believe that these benefits are due to suggestion, to psychic influence. There are two points that answer this objection: (1) If psychic influences can cure the disease, then the surgeon alone possesses this remarkable influence, because all surgical cases have been unsuccessfully treated by internists first. This compliment to the superior psychic power of the surgeon, unhappily the latter cannot conscientiously accept, because the surgeon is unable to favorably influence his patient excepting at the time of his contact with the patient on the operating table, and at that time his patient is unconscious. Then again the surgeon has seen equal improvement in cases whose glands were removed without the patient's knowledge. (2) If it is asserted that the great benefits of surgery are due to psychic causes, then the disease may be produced by psychic influences which would be precisely in accord with our main hypothesis. Against this hypothesis are also urged the following: That in Graves' disease there is a condition of hypothyroidism not a hyperthyroidism. This statement is based on the following: The iodine content of the thyroid is diminished in Graves' disease; there are in severe cases sometimes symptoms of myxedema, and the favorable results of surgical treatment are due to psychic influences and not to the diminution of the thyroid secretion. As to iodine content, Beebe found iodine in every case analyzed by him, though in severe cases the iodine was diminished in quantity. Now, on the theory here proposed there is an enormous increase in the call for iodothyroid, and a decrease of this element in the gland should follow an increased

use of it. Then, as Beebe has pointed out, the iodine, like the bile salts, circulates from the gland to the body and returns again without being excreted. Now, in Graves' disease the thyroid is enormously vascularized, and the blood circulates through it in much larger quantity, which would afford a much increased facility for the circulation of iodine between the rest of the body and the gland; still further, the amount of colloid in which iodine is normally stored is much diminished in Graves' disease.

There is, too, experimental evidence that there is another activating substance besides iodothyrin produced in the thyroid. This must be reckoned with, and finally, it must be borne in mind that in Graves' disease the body is h ghly sensitized to iodothyrin just as it is sensitized to psychic and painful stimuli; hence, even a diminished amount might easily produce a harmful effect, just as even minor psychic or physical stimuli may cause harmful effects. Besides, the administration of either iodine or thyroid extract not only gives no relief in Graves' disease, but causes an increase in the symptoms. This strongly speaks against the disease as being due to a diminished thyroid secretion.

In the late stage of the disease in which there is a physical wreckage of most of the organs of the body, including the thyroid itself, from the body wide stimulation, there may be an odd mixture of myxedema and Graves' disease; the body is like the charred remains of a partially burned building, whatever is done toward salvage the fire extinguisher is no longer needed; the fire (Graves' disease) has burned itself out. Some of these cases are benefited by small doses of iodine or of thyreoglobulin, but the dose must be cautiously given.

We do not know why only certain of the vast number of individuals subjected to emotional stimulation, to nerve strain, to infections, and to the other factors acquire the disease. This problem is like that of explaining why only certain individuals become insane after nervous strain or after infections; why only some under strain develop cardiovascular disease, and so throughout the entire gamut of diseases the ultimate truth is not known; our problem is that of the exciting cause and cure. When the truth is known it will likely appear that some reduced factor of safety, such as a disproportion of inorganic salts, or some general metabolic change, accounts for the thin ice through which the exciting causes break.

Now, in cases of Graves' disease the mere proposal to perform an operation becomes also a pathological excitation; this excitation may so much increase the disease that the patient is even less able than before to bring herself to submit to adequate treatment. On all sides this disease is beset by vicious circles, by pathological interactions. The ideal plan of approach, at least in my experience, is to assure the patient that hers is a curable

malady, that it can be treated in a hospital, and that non-operative measures will first be tried; then if they prove inadequate a simple operation will be done, that it will be best to leave this decision to the judgment of her medical adviser, and that since even the discussion of operation is both unpleasant and injurious, it would be best not to open this subject again. The patient usually gladly consents to leaving the whole matter to the judgment of the physician, and the way is then opened for the most effective treatment which in my judgment has ever been proposed—namely, ligation or excision on the new principle of *anociassociation*.

The anesthetist, a nurse, specially trained, gives fictitious inhalations under the precise conditions of regular anesthesia under the guise of "inhalations" supposed to be a part of the general treatment. Every morning the patient is given a sterile hypodermic. On the morning of the operation, which is performed in one of the favorable phases of the numerous cycles of the disease (on the morning of the day of the operation), the hypodermic will contain morphine and scopolamine, and instead of an oxygen "inhalation," nitrous oxid is added and the patient falls to sleep in her bed without the slightest knowledge or suspicion that the first step of an operation had already begun. The patient is then transported anesthetized to the operating room, where the operative field is prepared. Up to this point the patient's brain, hence, the remainder of the body, is in a negative state, and this is half of the innovation of the specialized operation; the other half is this, any injury of any sensitive part of the body, though the patient is under inhalation anesthesia, excites the brain, and hence through the brain all of the motor mechanism, especially the thyroid. Inhalation anesthesia is but a thin veneer, and although the patient is unconscious, the afferent impulses set up by the operation reach the brain apparently as readily as if no anesthesia were given.

This is the source of the hyperthyroidism, so-called, that constitutes the greatest danger of the operation. Operation under inhalation anesthesia on any sensitive part of the body produces precisely the same exacerbation of the disease (hyperthyroidism) as operations upon the thyroid gland itself. How may this be avoided? It may be wholly avoided by the use of complete local anesthesia, by the use of novocaine throughout the entire operation, just as completely as if the patient had received no general anesthesia. The patient has received no psychic stimulation arising from knowledge of the imminence of the operation, and none in being anesthetized, and finally, no afferent impulse reaches the brain from the field of operation—then not a single nocuous or harmful impulse reaches the brain—this state can be designated only by coining a new word, *anociassociation*. The result of operations performed by this method is scarcely credible; the condition of the patient at the end of the operation is precisely the same

as when in bed the day before. Indeed, this is the standard; unless the result equals this, there has been an error in the technique.

By this technique the scope of the operation is greatly increased, and the gland can be safely removed from any patient whose condition will endure the metabolic influence of the sudden withdrawal of so much active gland tissue. In such cases it is best to ligate the poles and later, if necessary, excise the lobe. This operation of pole ligation is done in bed without the patient's knowledge and in a few minutes.

In any case the operation is but a means to the end—namely, the raising of the threshold of environmental stimuli by diminishing the amount of activating sensitizing thyroid secretion and in conjunction with physical and psychic rest, permitting the patient to regain the power of normal control by the brain. Travel, diversion, nature, all are helpful, the operation serving to break the pathological change at one of its strongest links. These patients should be and can be literally taken by the hand and led away from mankind through the flowery paths of ease and pleasure to the haven of health.

SUMMARY. Graves' disease is not a disease of a single organ or the result of some fleeting cause, but is a disease of the motor mechanism of man, the same mechanism that causes physical action and that expresses the emotions; its origin is in phylogeny and its excitation is through either some stimulating emotion intensely or repeatedly given, or some lowering of the threshold of the nerve receptors, thus establishing a pathological interaction between the brain and the thyroid. This pathological interaction may be broken by diminishing the thyroid output, thus allowing the brain to regain normal control, or by securing physiological rest, which simultaneously secures normal control of the brain, which in turn will give the thyroid the opportunity of returning to the normal.

As to the effect of the operation of excision of a lobe or of ligation, the benefits are so striking and so uniformly successful in cases which are the despair of medicine that that point is settled beyond doubt. Because the conception here presented relates wholly to the release of energy it is designated the Kinetic Theory.

THE COMMONER FORMS OF RENAL DISEASE, WITH SPECIAL REFERENCE TO THE KNOWLEDGE OF THEM MOST USEFUL AT PRESENT TO THE GENERAL PRACTITIONER[1]

By Lewellys F. Barker, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, AND PHYSICIAN-IN-CHIEF, JOHNS HOPKINS HOSPITAL.

INTRODUCTION.

Every man in general practice sees, from time to time, patients suffering from renal disease. In my own experience, and, I believe, in the experience of many medical men, it has become clear that as regards the diagnosis of renal disease, mistakes are made in four main directions: (1) Serious renal disease, when present, may be entirely overlooked. (2) Urinary changes, due primarily to disease of other parts of the body, notably of the heart and arteries, may often be wrongly interpreted as evidences of primary renal disease. (3) There is an attempt among some to push the diagnosis of the exact form of renal disease present to a point beyond that to which we are, in reality, able safely to arrive by the clinical methods which have as yet been worked out. (4) More, perhaps, err on the other side and do not try to distinguish the different forms of renal disease, even when distinctions can easily and profitably be made among them clinically; thus, too often, do we find all renal diseases lumped together as "nephritis," no attempt being made to separate the degenerative, inflammatory, and circulatory nephropathies from one another or to ascertain the toxic or infectious etiological factors. Now, during the last ten years, especially, clinicians and pathologists have been working vigorously at the problems connected with renal disease, and certain real advances in our knowledge of these conditions have been made. Among the many studies which have been prosecuted and the results which have been achieved, I shall attempt, to make a selection of certain points which seem to me of greatest interest, and of greatest value, to men who are actually engaged in the practice of medicine. I shall pay most attention to: (1) The symptoms which indicate the existence of renal disease or which lead us to suspect it; (2) the commoner forms of renal disease clinically grouped; (3) the pathological anatomy of the commoner forms of renal disease; (4) the main etiological factors concerned; (5) the influence of experimental injuries to the kidneys on our conceptions of renal disease; (6) the conception of renal diseases based on

[1] An address delivered at the Annual Meeting of the West Virginia State Medical Association, held at Webster Springs, West Virginia, July 11, 1912.

the chemistry of the colloids; (7) certain functional tests for renal efficiency; and, (8) in closing, some therapeutic principles based on our present knowledge of renal disease.

SYMPTOMS WHICH INDICATE THE EXISTENCE OF RENAL DISEASE, OR WHICH LEAD US TO SUSPECT IT.

Under this caption I shall refer to (1) certain urinary changes; (2) the occurrence of edema; (3) certain vascular changes; and (4) certain phenomena referable chiefly to an intoxication of the nervous system, the so-called uremic symptoms.

The urinary changes to which I refer include (1) albuminuria; (2) cylindruria, or the presence of casts in the urine; (3) changes in the amount of urine (polyuria or oliguria); (4) nycturia, or rising at night to pass urine; (5) so-called hyposthenuria, the condition in which the kidney is no longer able to secrete a concentrated urine, rich in metabolic products and salt, the twenty-four hours' urine having, constantly, a lower specific gravity than normal; and (6) hematuria.

As is generally known, *albuminuria*, by itself, need not point to renal disease, for albumin may appear in the urine in various inflammatory affections of the lower urinary passages (pelvis of the kidney, ureter, urinary bladder, urethra); in such cases, pus is also present in the urine (pyelitis, cystitis, gonorrhea). In women, a leucorrheal discharge from the vagina, or menstrual blood, may be mixed with the urine and simulate an albuminuria. Even when the albumin comes from the kidney (true renal albuminurias) we have to distinguish between those due to serious renal disease, or to severe cardiac insufficiency, on the one hand, and those of very little clinical import, the so-called physiological albuminurias, including cyclic albuminuria and orthostatic albuminuria, on the other; in the latter group there may be an entire absence of other signs of renal disease (casts in the urine, heart hypertrophy, arterial hypertension, etc.).

The heat and acetic acid test and the cold nitric acid ring test suffice for all ordinary clinical purposes; for a quantitative estimate of albumin, a judgment based upon the precipitate obtained with the heat test may be accurate enough, though the estimation by Esbach's albuminometer is easily carried out.[2] It is generally believed that the albumin is given out by the glomeruli, not only

[2] In rare cases we are surprised to find a urine in which, on heating, an abundant precipitate of albumin occurs, while on heating longer, and to a higher temperature, the precipitate again goes into solution, to fall out once more on cooling. Should the physician meet with such a urine, he will know at once that he is dealing with the so-called Bence-Jones body in the urine, and he may feel sure his patient is suffering from some form of disease of the bone marrow, in all probability, myeloma. An *x*-ray examination of the bones in such cases will reveal the size and distribution of the tumors.

in glomerulonephritis, but also in renal diseases in which the glomeruli look histologically normal (for example, nephropathy of pregnancy).

The occurrence of *casts* in the urine (cylindruria) is of great help in indicating that an albuminuria is truly renal in its origin. Contrary to what we were long taught, however, the kinds of casts present (hyaline, granular, waxy, etc.), while easily differentiable from one another microscopically, are not of much help in distinguishing the various forms of renal disease from one another; an exception must be made in the case of blood-casts (*vide supra*).

A marked diminution or a great increase in the quantity of urine passed (oliguria, polyuria) always excites our suspicion regarding the function of the kidneys and should lead to a careful examination for other signs and symptoms of renal disorder. An *oliguria*, associated with albuminuria and cylindruria, and, especially, associated with hematuria, is a common symptom in organic renal disease, particularly in certain diseases of the glomeruli (for example, glomerulonephritis). But we should never forget that in failing heart the interference to the circulation in the kidney may lead to marked oliguria with albumin and casts in the urine, and that these signs may disappear entirely when the circulation has been restored and the stasis in the kidney done away with.

A persistent *polyuria*, with urine of low specific gravity, is often a sign, either of contracted kidney, or of diabetes insipidus. Polyuria also occurs in amyloid disease of the kidney, and in pyelitis. A polyuria with high specific gravity of the urine is rarely seen in renal disease; it is, of course, most often met with in diabetes. Temporary polyurias occur very frequently in a variety of conditions (for example, after drinking water; on the disappearance of an edema; in convalescence from acute disease; after taking diuretics).

In recording the history of a patient, it is always well to ask the question. "Do you have to get up at night to pass urine, and if so, how many times?" for this symptom (*nycturia*) is very common in renal disease, especially in beginning contraction of the kidney.

The term *hyposthenuria* I have already defined. The symptom is not often recognized in general practice, for, to observe it, the whole twenty-four hours' urine has to be collected, repeatedly, and the specific gravity thereof regularly taken. According to Schlayer, such a secretion of thin urine, hyposthenuria, can arise in two ways: either through lessened production of solid substances, or through increased production of water. In the first instance, the hyposthenuria appears to be due to an injury to the cells of the renal tubules; in the second instance, to an oversensibility of the renal vessels. Schlayer and his pupils speak, therefore, of a *tubular* and of a *vascular hyposthenuria*. The distinguishing characteristics of these two hyposthenurias are briefly these: In the tubular form,

the concentration remains permanently the same; it is always low. The addition of common salt to the food does not heighten the specific gravity, and the total amount of sodium chloride given out in the twenty-four hours cannot be increased by feeding common salt, since the tubules do not work adequately. In the vascular type, the concentration also remains permanently at the same height, but the specific gravity may be much higher than in the tubular type. Here, an addition of sodium chloride is quickly eliminated with increased output of water, but the concentration remains the same. The renal vessels, here, appear to be over-sensitive and to react to every secretory stimulus by producing larger amounts of water.

Renal *hematurias* (with formation of blood casts) are of considerable diagnostic importance, for they point definitely to diseased glomeruli. The glomerular affection may be either a diffuse glomerulonephritis due to soluble toxins in the blood, or a focal embolic injury of single glomeruli or single capillary loops in glomeruli due to bacterial emboli (*e. g.*, in endocarditis lenta, in sepsis with acute tonsillitis, and in other infections with bacteriemia).

Whether an *edema* is due to renal disease or to cardiac insufficiency or to some other cause (angioneurosis, anemia, cachexia) is sometimes hard to determine, The edema of renal origin seems to depend upon two factors: (1) upon an injury to the bloodvessels of the glomeruli of the kidney itself, either obstructing their lumina, or interfering with their capacity for contraction and dilatation, and preventing the excretion through the kidney of common salt and water in proper amounts; and, (2) a lesion of the small bloodvessels all over the body (especially of the skin and of the subcutaneous tissue), leading to increased permeability of the same. In contrast to the edema due to stasis (chronic heart disease), in which the influence of gravity, and distance from the heart, play a great role in the distribution of the edema, the edema of renal origin begins very often in the face, especially about the eyelids. A fact which is often overlooked is this: *the edema which occurs in the late stages of contracted kidney is rarely directly due to the renal lesion itself but is a true stasis edema due to beginning failure of the heart.* Now and then, in the course of contracted kidney, an edema directly renal in origin occurs, owing to the superimposition of an acute renal disease upon the chronic disorder.

The occurrence of *high blood pressure* (arterial hypertension) with *hypertrophy of the left ventricle* are very important signs and often lead us to investigate the functional power of the kidneys. A systolic blood pressure of 160, 180, or more, associated with hypertrophy of the left ventricle (apex beat displaced, downward and outward) should always make one think of the possibility of contraction of the kidney. We meet with such hypertension and cardiac hypertrophy especially often in patients of middle life who have

indulged freely in food and drink, though we sometimes see them also in abstemious individuals. In the absence of other factors accounting for the hypertension and the cardiac hypertrophy, one can be fairly sure that the condition is due to an atherosclerotic disease of the fine arterioles (in the sense of Jores) supplying the various organs of the body, including the kidneys, and leading, in the latter, to some contraction of the same. There may be only a trace of albumin in the urine with a few casts, the specific gravity is usually rather low; and the patients give, usually, a history of nycturia, sometimes lasting for years. The complaint of the patient on consulting the physician, however, is usually one dependent on the hypertension, or on the beginning cardiac insufficiency (headache, dizziness, dyspnea, fatigability, etc.).

It would appear that arterial hypertension with cardiac hypertrophy, in renal disease, may occur whenever the process of urinary secretion is largely interrupted throughout its whole cross-section, in any part of the kidneys, for example, (1) in diffuse glomerular nephritis, (2) in sublimate poisoning with diffuse necrosis and blocking of tubules, (3) in most contracted kidneys, especially in those due to atherosclerosis of the vasa afferentia.

The so-called *uremic symptoms*, referable to an intoxication of the central nervous system (headache, dizziness, vomiting, diarrhea, renal asthma, somnolence, disturbances of visions from albuminuric retinitis, convulsions, coma) may sometimes though rarely be those which lead the patient first to consult the physician. Unless a thoroughly systematic examination were made in such a case as a matter of routine, including an examination of the urine, and of the blood pressure, the cause of the nervous symptoms might be entirely overlooked, or wholly erroneously interpreted.

THE COMMONER FORMS OF RENAL DISEASE, CLINICALLY GROUPED.

If we leave out pyelitis, on the one hand, and chronic passive congestion (stasis) of the kidneys, on the other, the forms of renal disease commonly met with by the general practitioner may be subdivided into three great groups.

I. Cases of acute renal disease (or nephropathy), with or without, dropsy.

II. Cases of subacute or chronic renal disease (or nephropathy), with true "renal" edema occurring in their course.

III. Cases of chronic renal disease (or nephropathy), without "renal" edema, lasting perhaps for years.

The first group of cases are often designated as "*acute Bright's disease*," a scoop-net which includes a large variety of renal diseases histologically and etiologically very different from one another (for instance, embolic purulent nephritis, ascending purulent nephritis, acute glomerulonephritis, acute tubular degenerations, etc.).

Form of disease.	Amount of urine.	Color	Specific gravity.	Amount of albumin.	Sediment.	Duration.	Results, accompaniments, etc.
Stasis kidney.	Scanty.	Dark.	High	Slight or moderate	Urates; occasional casts and red blood cells.	As long as stasis lasts.	Cardiac death; infarctions.
Acute nephropathy.	Oliguria or anuria; rarely polyuria.	Dark, occasionally bloody	High to normal.	Usually large.	Abundant; red blood cells; white blood cells; granular, hyaline, blood and epithelial casts.	Weeks to months.	Uremia common; sometimes arterial hypertension; edema common.
Chronic nephropathy with renal dropsy (chronic parenchymatous nephritis).	Oliguria.	Dark.	High.	Large.	Abundant; all varieties of casts; fatty epithelium; red blood cells.	Death, a few months to one or two years; rarely healing with secondary contraction of kidney.	General anasarca. Heart hypertrophy. Usually increased blood pressure. Uremia common.
Chronic nephropathy without renal dropsy (contracted kidneys, most often arteriolar nephropathy).	Polyuria.	Pale.	Low, usually	Trace.	Very little; occasional cast or red blood cell.	Years; decades.	Progressive arterial hypertension to 220 or 260 or more; cardiac hypertrophy; no dropsy until myocardial insufficiency sets in. Death from apoplexy, uremia, cardiac failure, or, often, terminal infections.
Amyloid.	Normal or polyuria.	Pale.	Normal or low.	Variable; often much.	Slight; hyaline, granular, and waxy casts.	Months to years.	Marked edema usually; no uremia; normal blood pressure; no heart hypertrophy; chronic suppuration, tuberculosis or lues as etiology.
Pyelitis.	Normal or polyuria.	Turbid.	Normal or low.	Slight.	Pus cells; pelvic epithelium (casts only when complicated by pyelonephritis or other nephropathy).	Acute or chronic.	Fever; pain; etiology may be evident.
Cystitis.	Normal or oliguria.	Turbid, sometimes bloody.	Normal.	Slight, due to pus.	Slight; pus cells; red blood cells; squamous epithelium; triple phosphates.	Acute or chronic.	Alkaline urine; ammoniacal odor; complicated often by pyelitis and pyelonephritis.

The second group includes the cases often described as "*subacute Bright's disease*" or as "chronic parenchymatous nephritis" (large white and large variegated kidney).

The third group includes the *contracted kidneys*, not only the so-called "genuine" or "primarily contracted kidney" but also the so-called "secondarily contracted kidney" (see notes on pathology).

In the preceding table the characters of the urine, duration of the disease, the results, etc., are summarily tabulated.

NOTES ON THE PATHOLOGICAL ANATOMY AND HOSTOLOGY OF THESE COMMONER FORMS OF RENAL DISEASE.

The kidneys are perhaps the most important excretory organs of the body and they are frequently subject to injury. The injuries sustained vary in kind and degree according to the quantity and quality of the injuring agent, and its mode of entrance into, and exit from, the kidneys.

Each kidney must be thought of as a very complicated organ, made up of a whole series of *secretory units*, each unit consisting of its glomerulus and attached tubule (*parenchyma*), surrounded by bloodvessels and a certain amount of connecting tissue pertaining to that glomerulus and tubule and filling up the *interstices* between neighboring secretory units. Since single parts of the secretory unit and of the interstitial tissue may be separately diseased, the most variable clinical and pathological pictures arise. The study of renal diseases is made more complex by the fact, that, after an injury has been sustained, healing processes may go on for years; after death, we may see only the scars of some old process and be unable to form an accurate judgment as to the cause and course of the disease which preceded the scars.

The older pathological literature is permeated by the terms "interstitial" and "parenchymatous" diseases of the kidney. By the former, is usually meant involvement of the bloodvessels and the connective tissue of the organ; by the latter, involvement of the glomeruli and tubules themselves. Now, when patients suffering from acute disease of the kidney die and come to autopsy, it is sometimes clearly evident that the parenchyma, sometimes just as obvious that the interstitial tissue, has suffered predominantly; in chronic renal disease, where reparative processes have been going on for a long time, it is rare to find a process which is purely "interstitial," on the one hand, or purely "parenchymatous," on the other; both parenchyma and interstitial tissue have undergone alterations in varying degree.

One very important distinction among the pathological processes which occur in the kidney is that which divides them into *focal*

(scattered, or disseminated) lesions, on the one hand, and diffuse (widespread, almost universal) lesions on the other. In general, the more diffuse the renal disease, that is to say, the greater the area of kidney substance injured, the greater the danger of death in acute processes, and of early renal insufficiency should the patient live long enough for repair to set in. The disseminated (or focal) lesions, on the other hand, may cause very few symptoms at the time of their occurrence in the acute stages of the disease, and, when they go on to the healing stages, sufficient healthy renal tissue may remain to permit them to work fairly efficiently for a long time.

The processes described by pathologists as "interstitial" are most often due to disseminated or focal lesions, while the processes described by them as "parenchymatous" (glomerulotubular) are most often due to diffuse lesions. This makes it easy to understand why it is that patients with predominantly interstitial lesions may apparently recover entirely from a renal injury, or may live many years, without disturbing symptoms; whereas, in patients with predominantly glomerulo-tubular lesions, the prognosis is worse. As Aschoff and others point out, however, this is only a general rule, for if a diffuse injury affect only the epithelium of the renal tubules, leaving the glomeruli and bloodvessels intact, or nearly so, the organ may, by a regenerative process, become entirely normal again, provided the patient survive the acute insult. But extensive diffuse injury to the glomeruli seems rarely, if ever, to be wholly recovered from; it leads easily to permanent insufficiency of the kidneys, though, compensatory processes may be advantageously operative, for a time, before the final decompensation sets in.

The attempts which have been made sharply to distinguish *glomerular* lesions from *tubular* lesions, in diseases of the renal parenchyma, are praiseworthy and have undoubtedly enriched both clinical and pathological knowledge. But we must keep ever in mind the fact, that, on the one hand, loss of epithelium often leads to proliferative changes in the connective tissue which constricts the tubules and causes retention cysts with atrophy of glomeruli, while, on the other hand, an injury destroying a glomerulus can lead to "inactivity atrophy" of a tubule, and when we recall the various regenerative and hypertrophic processes which may complicate the histological picture in chronic cases, it is easy to see how difficult to decipher a given end stage may be. We can only be grateful that men like Councilmann, Christian, Dickson, Ewing, MacNider, Mallory, Ophüls, Pearce, Welch, and Winternitz, in this country, and Aschoff, Herringham, Thursfield, Heineke, Jores, v. Kahlden, Langhans, Löhlein, Reichel and Ribbert, in Europe, have done, and are doing, so much to solve the histological difficulties by which we are confronted. From what I have said regarding parenchymatous and interstitial lesions, regarding

injury to the glomeruli and harm to the tubules, and concerning focal and diffuse processes, involving these organs, it is obvious that the unravelling of a process by histological study can be no easy task.

The time has come, I think, when clinical men and pathologists should be very cautious in the use of the word "nephritis," since if in accordance with the best usage at present, we limit the meaning of this word definitely to inflammations of the kidney, the term "nephritis" is by no means synonymous with the term "renal disease" or "nephropathy." The latter is a much more inclusive term, embracing, as it does, not only inflammation of the kidney (nephritis), but also any disease of the kidney, be it inflammatory, degenerative, or circulatory in origin.

Let us take the diffuse hematogenous nephropathies, that is, the diffuse renal diseases due to some noxa brought to the kidneys by the blood, as an example. In one set of them, the tubules of the kidneys are chiefly affected, the glomeruli being much less or not at all involved. Here we have to deal with a toxic degeneration of the epithelium of the renal tubules, rather than with an inflammation (nephritis). Examples of such toxic necroses, or degenerations, of the renal tubules are seen in the kidney of phosphorous poisoning, that of corrosive sublimate poisoning, and the renal disease which occurs in pregnancy. On the other hand, a soluble poison brought to the kidneys by the blood may cause true inflammation of nearly all the glomeruli of the kidney, the so-called "glomerulonephritis." A typical example is the severe form of acute nephropathy which so often complicates scarlet fever.

The toxic degenerations of the renal epithelium, though giving rise to acute nephropathies, need not necessarily be fatal. Indeed, if the intoxication cease, the patient may recover completely. This is especially true of the intoxication of the kidney which sometimes occurs in pregnancy. As soon as the uterus is emptied, the intoxication ceases and the patient as a rule recovers promptly. In cases of cure after necrosis of the epithelium in sublimate poisoning, the epithelium of the kidney is regenerated.

Every practitioner is familiar with patients who have had acute renal disease and recovered. We have to distinguish carefully, however, those who become entirely well, from those who only apparently get well, but who, actually, still have progressive lesions and who succumb, later on, to chronic renal disease. In the latter cases, we have to deal, in the acute attack, usually, with milder forms of glomerulonephritis, associated with a tubular injury, in which recovery is incomplete, the reactive processes leading gradually to a "secondary contraction" of the kidney. Many acute, focal, inflammatory lesions doubtless heal and never give rise, either in the acute stage, or during the period of repair, to any serious symptoms.

In the cases of our second clinical group, so-called subacute

Bright's disease or chronic parenchymatous nephritis, we have to deal nearly always with extensive glomerulonephritis, with tubular degenerations, combined with extensive processes of repair. The inflammatory and reparative processes are diffuse. There are two groups of cases: (1) that in which there is marked desquamation and proliferation of epithelium and capsule of the Malpighian tufts ("stormy type" of Löhlein; desquamative type of v. Kahlden) and (2) that in which the phenomena mentioned are not prominent, the histological changes consisting chiefly of enlargement of the glomeruli, the loops of which are crowded with cellular elements of the endothelial type ("milder type" of Löhlein; thrombosing type of v. Kahlden; intracapillary glomerulitis of American writers). Such subacute, diffuse, inflammatory, nephropathies lead, usually within a year or two, sometimes in a month or two, to a fatal termination; in rare instances, where the injury has been less complete, there may be gradual healing with secondary contraction of the kidney; then the patients may live for years without troublesome symptoms, until, later on, uremic symptoms appear, or cardiac failure sets in.

Recent studies have thrown much light upon the nature of the different forms of "contracted kidney." The contracted kidney is always the end-stage of some earlier process, and we know now that a series of processes, entirely different from one another in the beginning, may give rise to similar end-stages, namely, contracted kidneys. It would seem probable, from newer studies, that only in a small percentage of the cases are contracted kidneys to be regarded as the end-stage of a preceding nephritis. I mean, of a glomerulonephritis. Occasionally, too, contracted kidneys result from an earlier embolic (focal) nephritis, or from the healing of an interstitial nephritis (Aschoff). But there is growing evidence for the belief that many contracted kidneys are renal atrophies of circulatory origin, due to *atherosclerosis of the small arterioles supplying the kidney;* it is thought that this arteriolar-sclerosis, a part of a process affecting the organ-arterioles generally throughout the body, leads to lessened blood supply to great numbers of glomeruli, to hyaline degeneration of the same and to inactivity atrophy of the corresponding tubules — the totality of changes accounting for the gradual skrinking of the kidney. This form of contracted kidney, some authors assert, should not be regarded as a "nephritis" at all, but as an atrophic nephropathy, the result of arteriolar change.

There is another form of atherosclerotic kidney in which, owing to severe atherosclerotic disease of single arterial stems, there is "patchy" atrophy and contraction, with very coarse granulation of the surface of the kidney (Ziegler); this form is that usually spoken of in the text-books as the "atherosclerotic kidney," while the disease described above as probably due to atherosclerosis of the small organ arterioles rather uniformly throughout both

kidneys, is usually referred to, in the text-books, as "genuine contracted kidney." This conception of "genuine contracted kidney," championed especially by Jores and his pupils, would seem to be a return to the English idea, advanced years ago by Gull and Sutton and later supported and extended by Johnson, that contracted kidneys are the result of "arterio-capillary fibrosis." The changes in the small arteries of the organs can be made out even in cases of beginning contraction of the kidneys, in middle and later life, in which death has occurred from cerebral hemorrhage, after a period of extreme arterial hypertension with cardiac hypertrophy (Löhlein).

FACTORS CONCERNED IN THE ETIOLOGY OF THE COMMONER FORMS OF RENAL DISEASE.

From the etiological side we may divide the renal diseases or nephropathies into two great groups: (1) Those due to injuries reaching the kidneys through the blood, the so-called *hematogenous* or *descending nephropathies*, and (2) those due to injuries reaching the kidneys through the urine, the so-called *urinogenous* or *ascending nephropathies*.

The hematogenous nephropathies may, in turn, be divided into (*a*) those which are *diffuse* and (*b*) those which are *focal*. The former are due to soluble toxic substances circulating in the blood, the latter to organized particulate substances, namely bacteria.

The *diffuse hematogenous nephropathies*, due to soluble toxic substances, are further analyzable on the etiological side, and here it is interesting that the different soluble toxins seem to be to a certain extent, selective, regarding the particular structures of which the kidney is made up. Thus one set of toxins picks out the epithelial cells of the tubules, another has a selective effect upon the glomeruli, and a third group, apparently, upon the small arterioles of the organs, especially upon the vasa afferentia.

Tubular degenerative nephropathy may be due to a whole series of soluble poisons, including corrosive sublimate, phosphorus, potassium bichromate, the poisons produced in the uterus of the pregnant woman, the toxins of cholera, yellow fever, and of other acute infections, and hemoglobin.

The sublimate kidney has been carefully studied by A. Heineke, the phosphorus kidney by Landsteiner, the pregnancy kidney by several observers, the cholera kidney by E. Fraenkel, the yellow fever kidney by Councilmann, and by Marchoux and Simond, and the hemoglobin kidney by J. E. Schmidt.

The toxic affections of the glomeruli (*glomerulonephritides*) may be acute, subacute, or chronic and may be of the desquamative (or catarrhal) form, or of the intracapillary (or thrombosing) form. But in all cases, the commonest etiological factor seems to be a

streptococcus toxin. This form of nephropathy is most common after scarlet fever, tonsillitis, and other forms of streptococcus infection. It would appear that the toxins in pneumococcus infection, and in typhoid fever, can sometimes cause a glomerulonephritis. In Löhlein's series, by far the commonest etiological factor was preceding streptococcus sore throat. It is not improbable that the glomerulonephritis which sometimes complicates diphtheria, tuberculosis, dysentery, and certain other infections may be due to complicating streptococcus infection, with absorption of streptococcus toxins into the blood, through which they reach the glomeruli. The frequency of this form of nephropathy following exposure to cold may stand in relation to streptococcus sore throat. In the outspoken forms of so-called parenchymatous nephritis, where there is a combination of glomerulonephritis with degenerative tubular nephropathy, the same etiology (streptococcus toxin) seems to be commonest.

Whether the arteriolar nephropathy, which gives rise to the genuine contracted kidney, depends upon the action of soluble toxins upon the vasa afferentia directly, or is secondary to an arterial hypertension, which in turn is kept up by some general intoxication, is not yet satisfactorily known. The relation of this form of arteriolar disease to the excessive use of food and alcohol, is interesting.

If we turn now to the etiology of the *focal hematogenous nephropathies*, we shall find that they depend upon bacteriemias, with lodgement of single bacteria or groups of bacteria, in the kidney substance, namely in individual glomerular loops, in blood capillaries among the renal tubules, or passing through these, in the interstitial tissue of the kidney, or by excretion into the kidney tubules, where multiplying, they may form bacterial casts.

At least two forms of *embolic nephritis* can be distinguished—an embolic purulent nephritis, due to streptococci, or staphylococci, and an embolic, hemorrhagic (non-purulent), glomerulonephritis, due to embolism of single bacterial loops in the glomeruli by the streptoccocus viridans in endocarditis lenta.

What the organism is in the acute interstitial nephritis which Aschoff has described after scarlet fever, in which the cellular exudates consist of cells resembling lymphocytes, is not known. The excretory form of hematogenous bacterial nephritis has been especially studied by Orth. Here the bacteria reaching the kidney by way of the blood may be excreted through the glomeruli, or perhaps through the tubules, into the lumina of the tubules, where they may multiply and give rise to bacterial casts. As the urinary flow is slowed in the portions of the tubules situated in the medulla of the kidney, these casts are found in that region, and the soluble toxins that the bacteria produce give rise to necroses and purulent inflammations near the apex of the pyramid; hence the name given by Orth to this form of nephropathy (nephritis papillaris mycotica).

The *urinogenous or ascending nephropathies* are divisible into two great groups (*a*) the hydronephrotic nephropathies and (*b*) the pyelonephritides.

The hydronephrotic nephropathies are due to pressure of urine owing to obstruction in the urinary passages (renal calculus, ureteral obstruction, prostatic hypertrophy, stricture of the urethra, etc.). Such hydronephrotic nephropathies may, obviously, be either unilateral, or bilateral, according to the seat of the obstruction.

A pyelonephritis may be due to any one of the pyogenic organisms, though it is most often, perhaps, dependent upon the Bacillus coli communis. Not infrequently the tubercle bacillus is the cause, and, in some cases, we have mixed infections of tubercle bacilli and pyogenic microörganisms.

In the following table I have tentatively classified the commoner forms of nephropathy, according to their pathology and etiology:

I. Renal Diseases Due to Injuries Reaching the Kidneys through the Blood (Hematogenous, or Descending Nephropathies.)

A. Diffuse hematogenous nephropathies due to soluble toxic substances.

(*a*) Tubular degenerative nephropathies (*e. g.*, sublimate kidney; phosphorus kidney; bichromate kidney; pregnancy kidney; hemoglobinuric kidney; kidney of cholera, yellow fever and other acute infections).

(*b*) Glomerulonephritis (acute, subacute, chronic), due most often to streptococcus toxins.

(1) Catarrhal form with desquamation and proliferation of capsular epithelium.

(2) Intracapillary or thrombosing form of glomerulitis.

(*c*) Arteriolar nephropathy (chronic), probably due to action of toxic substances on organ arterioles, causing atherosclerosis of vasa afferentia.

B. Focal hematogenous nephropathies due to bacteriemias.

(*a*) Embolic (purulent) nephritis from streptococcus and staphylococcus.

(*b*) Embolic hemorrhagic (non-purulent) glomerulonephritis (large red or variegated kidney due to streptococcus viridans).

(*c*) Acute interstitial nephritis with lymphocytic exudate after scarlet fever.

(*d*) Excretory bacterial nephritis (*nephritis papillaris mycotica* of Orth) (casts of cocci).

II. Renal Diseases Due to Injuries Reaching the Kidneys through the Urine (Urinogenous, or Ascending, Nephropathies).

(*a*) Hydronephrotic nephropathy (due to obstruction in urinary passages) depending on renal calculus, ureteral obstruction, prostatic hypertrophy, stricture of urethra, etc.; may be unilateral or bilateral.

(*b*) Pyelonephritis.

(1) Pyogenic.

(2) Tuberculous.

THE INFLUENCE OF EXPERIMENTAL INJURIES TO THE KIDNEYS ON OUR CONCEPTION OF RENAL DISEASES.

Most hopeful for our future knowledge of renal disease is the increasing tendency to solve the problems connected with them by resorting to experiment. During the last ten years, the results of many researches, thus specifically directed, have been reported, and not only has our knowledge of the pathological anatomy and histology of renal disease been furthered, but also that concerning the function of individual parts of the kidney and the way these functions are disturbed in lesions of different kinds, have been increased in a most gratifying way. New light has been thrown upon the functions of the glomeruli on the one hand, and upon the tubules on the other, and we are rapidly getting a clearer insight into the nature of renal edema, of oliguria, of anuria, of polyuria, and of the relations of renal disease to arterial hypertension, to cardiac hypertrophy, and to uremia.

I can scarcely do more than direct attention to the bare outline of the work that has been undertaken and accomplished. To those who are interested in following the subject further, I can heartily recommend the perusal of Dr. Richard M. Pearce's Harvey Lecture on "Experimental Nephritis."[3] in which the subject is presented in a particularly clear and illuminating manner, and where full references to the bibliography are to be found. To those who rejoice at the progress of medical research in America, it is especially satisfactory to find so many American names among the contributors on the experimental side: H. A. Christian, E. C. Dickson, H. Emerson, M. C. Hill, T. C. Janeway, Jr., G. Lyon, S. J. Meltzer, W. Ophüls, R. M. Pearce, J. H. Austin, A. B. Eisenbrey, T. Sollmann, W. B. MacNider, H. P. Sawyer, J. A. Sampson, etc.

The attempts to produce pure tubular lesions by means of epithelial poisons (uranium nitrate, the chromates, corrosive sublimate)

[3] Archives of Internal Medicine, 1910, v. 133–167.

and pure glomerular lesions by means of vascular poisons (arsenic, cantharidin, venom) have in animals been fairly successful. With diphtheria toxin, it is possible to produce an experimental renal disease in which both the glomeruli and the tubules are severely injured. The more recent studies indicate that uranium nitrate, though it injures the tubular epithelium predominantly, injures also, to a certain extent, the glomeruli.

The investigators of experimental renal disease depended at first too much upon the results of histological study as a control. Since the application of functional as well as histological methods to the study, opinions regarding the exact effects of individual poisons upon the kidney are being modified. The observations of Takayasu, particularly, have revealed the fact that there may often be severe disturbances of function of a part of the kidney when there is little or no evidence of histological lesion there.

Especially instructive on the functional side are the observations of Schlayer and his pupils, working in Romberg's clinic, regarding the vascular reactions of the two main types of experimental renal disease, namely of glomerulonephritis and of tubular injury. This investigator and his associates have studied carefully the reaction of renal bloodvessels to various stimuli, after these different kinds of injury; they have investigated the relations of the particular injuries to the general blood pressure on the one hand, and to diuresis on the other, studies which have been carefully controlled in this country by Pearce.

More or less successful attempts are being made to ascertain the exact points in the normal kidney in which the various constituents of the urinary sercetion are put out (water, sodium chloride, nitrogenous substances like urea, uric acid, etc.). *It would appear that each individual substance which comes out in the urine is subject to its own laws of excretion, and that we must be extremely careful not to transfer the findings regarding the excretion of one substance to the excretion of another, even though it may seem to be closely allied, chemically, to the former.* This opens up a large field for experimental work; for each substance will have to be studied in its excretion-relations, under a whole series of experimental pathological conditions, as well as in various clinical states. There is a good deal of evidence, too, that in pathological states, functions ordinarily carried on by certain of the histological constituents, may when they are diseased, or destroyed, be taken up by other histological constituents, which ordinarily are not concerned with them. This "give and take" theory of renal function has been emphasized, especially by J. McCrae.

The view held at present, that renal edema depends upon diminished glomerular permeability on the one hand, and increased permeability of the cutaneous vessels, on the other, has already been referred to.

It marked a great step forward when P. F. Richter, in 1904, showed us how, experimentally, to produce, in animals, a nephritis accompanied by dropsy, thus reviving interest in the important but long overlooked observation of Chittenden and Alexander Lambert, in 1899, of the occurrence of ascites in uranium poisoning, and of Woroschilsky, in 1890, of general edema and dropsy in the same poisoning. With the new experimental method easily available, the questions of the influence of water retention, of salt retention, of renal vascular injury, of cutaneous vascular injury, etc., could be vigorously taken up, and while opinions are not yet fully in accord regarding these various points, there is every reason to believe that investigations are on the right path, and that before long many of the debatable questions will be satisfactorily answered. It seems certain now that in edema there is injury not only to the kidneys, but also to the bloodvessels all over the body. In getting rid of edema, we have to consider both components.

Not the least interesting, on the experimental side, are the researches dealing with the relation of arterial hypertension and cardiac hypertrophy to experimental renal disease. The well established clinical relations have received support, on the experimental side, through the observations, of Paessler and Heineke, bearing upon changes in the blood pressure after experimental reduction of kidney substance in the body, and through the careful studies of Carrel and Janeway in the same direction. These observations show, that when the amount of kidney substance is reduced beyond a certain limit, hypertension results. They do not, however, explain the exact mechanism by which the hypertension arises, and speculation is still rife as to the pathogenesis. The majority assume a toxic influence leading to the hypertension, though some accept the glomerular reflex theory of A. Loeb.

While the loss of large numbers of glomeruli, or injury thereto, results in arterial hypertension, extensive epithelial injury (tubules) without glomerular lesions, seems to result sometimes in hypotension. Interesting in this connection are the observations of R. M. Pearce, who found that the depressor substances normally present in the urine disappear from it after experimental injury to the epithelium of the tubules.[4]

The study of the origin of uremic symptoms, in renal disease, is the part of the subject which has thus far been least advanced by experimental work. While in experimental animals it is sometimes possible to produce gastro-intestinal disturbances with associated respiratory and circulatory symptoms, ending in coma and

[4] Great difficulty has been encountered in producing, experimentally, a chronic nephritis comparable to chronic nephritis in man. Thus far, the experiments of E. C. Dickson have been most successful in this direction. It is reasonable to assume that it will be easier to produce, experimentally, a chronic glomerulonephritis with secondary contraction than the so-called primary contraction (arteriolar nephropathy).

death, as yet no satisfactory explanation of the origin of these symptoms has been given and experiment has contributed nothing that we did not already know from clinical observation. That this dark corner of renal pathology will later on be lighted up, as the result of experimental inquiry, there can be no reason to doubt.

When progress is making so rapidly in many different directions in experimental renal pathology, great caution must be observed in transferring the results, uncritically, to human pathology. As to the conditions in human beings, the last word must be left to studies in the clinic.

CONCEPTIONS OF RENAL DISEASES BASED ON THE CHEMISTRY OF THE COLLOIDS.

Very recently, an attempt has been made to approach the problems of the nephropathies, both clinically and experimentally, from the starting point of colloid chemistry. The latter is a brand-new science. When the present generation of physicians was in training, the chemistry of the colloids was only making a beginning, but during the last fifteen years, advances in knowledge concerning the colloids have been made with such great rapidity, that text-books, presenting only an epitome of the subject, today, make large volumes.[5]

In the future, a training in the medical sciences must include, besides a knowledge of the physico-chemical laws which govern the crystalloids, a thorough grounding in the principles and facts of colloid chemistry. For the world of biological phenomena is both crystalloidal and colloidal in nature, and colloidal chemistry has the task of doing for living organisms what physical chemistry has done and is doing for the crystalloid world. This is obvious when we recollect that the proteins of the body, as well as its lipoids, and its carbohydrates, making up the cells and the details of their histological structure, and even the blood plasma, are in a colloidal state. Colloidal states of substances are met with sometimes in a liquid form, when they are known as *sols*, sometimes in a solid form, when they are known as *gels*.

Substances in a colloidal state, at least in their typical examples, are "heterogeneous systems," that is to say, they are spatial combinations of coexisting phases (for example, solids with liquids, or liquids with liquids). These phases are so in contact with one another that the surface relations are extremely large, that is,

[5] Pösch (V.), Introduction to the Chemistry of Colloids, English translation by H. H. Hodgson, 1910; also, Zsigmondy's Colloids and the Ultramicroscope, (Wiley) 1909; Pauli (W.), Physical Chemistry in the Service of Medicine, translated by M. H. Fischer, New York, 1907; Bechhold (H.), Die Kolloide in Biologie und Medizin, Dresden, 1912; also Zsigmondy (R.), Kolloidchemie, ein Lehrbuch, Leipzig, 1912; Ostwald (Wo.), Grundriss der Kolloidchemie, Dresden, 1909; Freundlich (H.), Capillarchemie und Physiologie, Leipzig, 1909; Müller (A.), Allgemeine Chemie der Kolloide, Leipzig, 1907.

there are an enormous number of scattered particles in a given volume of fluid. Moreover, the phases within the system are so distributed that the whole system gives the impression of being homogeneous. Such heterogeneous systems, with these two peculiarities (great surface development, and external appearance of homogeneity), are known as *dispersoids*. The one phase, consisting of separate particles scattered through the other phase which is a continuous substance, is called the *dispersive phase*, while the continuous substance itself, is called the *medium of dispersion*. The colloidal particles of a dispersive phase vary in size; some of them (the larger ones) are of a size corresponding to the lowest limit of microscopic visibility (0.1 micron), others, (the smaller ones), approach in size the lowest limits of ultra-microscopic visibility (0.001 micron), ultramicroscopic particles being those which are too small to be directly visible, but large enough to scatter, and polarize, a beam of light; the very smallest particles in a colloid state seem to approach in size the larger molecules of crystalloid substances—the transition-area between the colloid and the crystalloid world. When the dispersive phase consists of the larger particles, we have to deal with the so-called "dispersions proper" (including colloidal suspensions and colloidal emulsions), when it consists of smaller particles we have to deal with the so-called "colloidal solutions;" when a dispersive phase consists of particles smaller than 0.001 micron we have to deal no longer with colloid states, but with crystalloid solutions (molecular dispersoids and ionic dispersoids). In colloidal suspensions, the dispersive phase is solid, the medium fluid; in colloidal emulsions both phases are fluid. The same chemical substance may sometimes exist as a suspension-colloid, at others as an emulsion-colloid.

Partly responsible for the peculiar behavior of substances in colloidal state, are the tremendous surface energies which they develop and which have chemical, physical, and electrical importance. In this surface-energy, the capacity-factor is the size of the surface, the intensity-factor is the surface-tension. If one recalls the way the gases oxygen and hydrogen may be concentrated and chemically united on the surface of finely divided platinum, platinum sponge (as contrasted with the minimal influence of an equal weight of solid platinum), it will serve as an example of the effect of surface energy and its transformation through volume energy into chemical energy. Other interesting examples of absorption are seen in the capacity shown by certain colloids to take finely divided substances out of solution and to hold fast to them; such adsorption phenomena appear to be significant in connection with the behavior of lecithin, and of ferments, in the animal body.

Substances in colloidal state (dispersions proper) differ from the molecular dispersoids or crystalloids (like solutions of NaCl, sugar, etc.) in that they do not diffuse on dialysis, because the dispersive

phase consists of particles too large to pass through the pores of parchment paper or animal membrane. They have less Brownian movement and very little velocity of diffusion, and so have only a very slight osmotic pressure, or none at all. The internal friction, or viscosity, varies in different colloidal states; in emulsoids, it may increase rapidly with concentration, or change in temperature so as to pass from a fluid to a jelly.

All colloidal particles in the dispersive phase are electrically charged. Since the electrically charged particles mutually repel one another, the colloids remain in solution or suspension, and if the electrical charge be taken away, precipitation occurs. It is interesting that the electrical charges can be taken away by the addition of electrolytes. Further, on passing an electric current through a colloid, the charged particles, according as they are negatively or positively charged, will wander toward the anode or cathode (cataphoresis).

Life depends upon the existence of substances in colloidal states in the body-cells. In physiological and pathological processes, colloidal states undergo many "changes of condition." Thus sols are often converted into gels, (process of gelatinization). The process, in true gelatinization, is reversible; the gels can again be converted into sols and we may have to deal with alternating gelations and liquefactions. The process of gelatinization is closely allied to the phenomena of "swelling" or "imbibition," that is, to the property possessed by many substances to take on a jelly-like form (or emulsoid state) when placed in contact with fluid.

Now, the amount of water in every cell, the "turgescence of the cell," and the extent to which the cell constituents may pass from a *gel* to a *sol* state, or from *sol* to *gel*, are determined by properties peculiar to colloids. Thus protein substances have a specific avidity for water, varying with the conditions under which the colloid is placed. For example, both acids and alkalis change the avidity for water—increasing it; while salts may either increase, or decrease, the capacity to take up and hold water. It appears that bromides, nitrates, chlorates, and chlorides increase the capacity for swelling, the bromides most, the chlorides least; while acetates, citrates, tartrates, and sulphates decrease the capacity for swelling, the acetates least, the sulphates most.

On account of this important relation of acids and alkalies to the swelling capacity, I desire to call attention to some most important studies made by L. J. Henderson, of Cambridge, Massachusetts. He has tried to detect how it is that the blood is neutral and retains its neutrality against much acid or alkali. Henderson's studies seem to me to be of the greatest importance for the whole doctrine of equilibrium between bases and acids in the animal organism.

The body behaves as though it were very eager to preserve this equilibrium, and, in the preservation, it makes use of two sets of regulatory mechanisms, one internal and one external, which overcome the acidity which metabolic changes tend to produce.

In the internal mechanism, the blood, the tissue cells, and the tissue juices are concerned. Here, there is a chemical regulation, through which neutrality is maintained, largely by means of the phosphates and carbonates ("Henderson's factor"), partly by means of the proteins (acting as amphoteric electrolytes to neutralize either acids or bases, according to need, by dissociating in the one case as bases, in the other as acids.)

In the external mechanism, the functions of various secretory glands are concerned; thus, (1) through the excretion of CO_2 by the lungs, (2) the excretion of acid sodium phosphate, of uric acid, and of CO_2 by the kidneys, and (3) the excretion of acid in the sweat, the body possesses important means for getting rid of an excess of acid.

Now, in pathological states the tissues of an organ, owing to the action of toxins, or to circulatory changes, may conceivably accumulate acid in excess.

In several publications Martin H. Fischer,[6] of Cincinnati, has boldly pushed forward a conception of nephritis based upon colloid chemistry, on the one hand, and upon a disturbance of the equilibrium between acids and bases in the organism, on the other. He asserts that all the changes that characterize "nephritis" are due to a common cause; namely, to the abnormal production or accumulation of acid in the cells of the kidney. Resulting from this excessive acidity there is abnormal swelling of the tissue structures, which accounts, in his opinion, for the albuminuria, the cloudy swelling, the formation of casts, the quantitative changes in the urine, and the changes in the amounts of dissolved substances excreted. He supports his ideas by experimental work in animals and by clinical observations on human beings.

Applying what has been said above regarding the action of neutral salts upon the swelling capacity, Fischer believes that he has experimentally counteracted the effects of abnormal acidity in the kidney by the action of neutral salts, thus restoring normal structure and function. For example, by injecting HCl, alone, into animals he could produce an acute nephritis, whereas the same amount of HCl, injected along with concentrated solution of sodium chloride, caused no nephritis.

Fischer reports a number of clinical cases, some of them very severe with anuria and coma, and asserts that they made a rapid recovery by treatment with sodium carbonate and sodium chloride given per rectum.

Fischer's views have called forth rather severe criticism from a

[6] See especially his volume on "Edema," and another on "Nephritis."

high source,[7] partly, it would seem, on account of the dogmatic way in which the views have been presented, and his neglect adequately to value studies of the nephropathies made by other methods.

Personally, I am very much interested in Fischer's conceptions, though perhaps more in the starting point of his experiments than in any goal thus far reached. I think he may be doing a very real service in emphasizing the importance of studies in physical and colloid chemistry for the further investigation of normal and pathological renal phenomena, and I hope that experimenters trained in physical and colloid chemistry may coöperate actively with other investigators, trained in the methods of renal investigation hitherto used, to extend our knowledge of renal function and renal disease.

I may say that some (as yet unpublished) studies of Dr. A. W. Sellards, who is in charge of the chemical division of the laboratory in the clinic in which I work, indicate that, in a certain proportion of nephropathic patients, a very much larger amount of sodium bicarbonate has to be injected into the blood to make the urine alkaline than is required in normal individuals; but there are also many nephropathic patients, he finds, who respond by an alkaline urine to quantities of sodium bicarbonate (introduced intravenously), no larger than those required to make the urine alkaline in normal individuals.

It is interesting to note that von Hoesslin[8] found that the administration of sodium bicarbonate in rather concentrated solution led to a decrease in the albuminuria, in cases of renal disease studied by him; and it may be worth pointing out that Straub and Schlayer[9] have shown that the carbon-dioxide tension of the blood may stand in relation to the amount of albumin excreted by the kidneys, at least in certain forms of albuminuria.

ON CERTAIN FUNCTIONAL TESTS APPLIED TO THE KIDNEYS.

Through the researches of Albarran, Israel, Caspar and Richter and von Koranyi, various methods of testing the functional efficiency of one or both kidneys have been worked out. Some of these methods have been helpful, especially in the determination, in unilateral renal disease requiring nephrectomy, of the functional efficiency of the kidney on the other side, the urine being collected separately, by ureteral catherization.

The phenolsulphonephthalein test, introduced by Rowntree and Geraghty,[10] is the most important recent addition to our methods

[7] Archives of Internal Medicine, 1912.
[8] Deutsch. Arch. f. klin. Med., cv, 147.
[9] Münch. med. Woch., 1912.
[10] Archives of Internal Medicine, 1912, ix.

for measuring the functional efficiency of one, or both of the kidneys. To insure free secretion, the patient is given from 200 to 400 c.c. of water, twenty or thirty minutes before making the test. The bladder is emptied by aseptic catheter, the exact time noted, and 1 c.c. of the test solution (= 0.006 gram of the chemical) is injected intramuscularly, in the lumbar region. The urine, as it drops out of the catheter, is collected in a test-tube containing a drop of NaOH solution (25 per cent.), until a faint pinkish tinge appears (time noted). The catheter may then be withdrawn, and the patient voids at the end of one hour, and again at the end of two hours, each voiding being separately collected. The amount of phenolsulphonephthalein in each is quantitatively determined by means of a colorimeter, after taking the specific gravity, rendering the specimen alkaline with NaOH, and diluting it to one liter with distilled water. With Rowntree and Geraghty's modification of the Autonrieth-Königsberger colorimeter, the percentage can be read off at once, by noting the position of the indicator on the scale.

Normal individuals excrete from 50 per cent. to 65 per cent. (average 57.5 per cent.), in the first hour. When renal efficiency is impaired, the output may be, quantitatively, greatly decreased, and the excretion is delayed.

The test can be used, either to estimate the total excreting function, in bilateral renal disease, or for a comparison of the efficiency of the right kidney with that of the left, in unilateral disease. In the medical and genito-urinary clinics at the Johns Hopkins Hospital, Drs. Rowntree and Geraghty have made many tests which establish the clinical value of the method. During the last year Dr. Helen Watson has applied the test, in the medical clinic, in over 100 cases, with confirmatory results, and, at the suggestion of my colleague, Dr. Thayer, Drs. Rowntree and Fitz have carefully compared the findings after the phenolsulphonephthalein test, in a series of cases, with those after Schlayer's tests, (KI. lactose, and NaCl).

Schlayer and Takayasu, of Romberg's clinic, are of the opinion, as a result of their experimental and clinical work, that NaCl and KI are excreted by the epithelium of the renal tubules, and that lactose and water are excreted by the glomeruli. In experimental nephropathies (1909), they found that destruction of the tubular epithelium resulted in impaired excretion of NaCl and of KI; the greater the injury, the worse was the excretion. In these cases, the renal bloodvessels, they assert, were uninjured, and water and lactose were excreted in much the same way as by the normal kidney. In the animals in which the renal vessels (glomeruli) were injured, the excretion of lactose was found, by them, to be delayed.

They then applied these tests to human beings, not to determine the sufficiency or insufficiency of the kidneys (as regards their

eliminating power for the total needs of the body), but rather for the purpose of gaining an insight into the mode of working of diseased kidneys, and to ascertain what changes in the functions of tubules, or vessels, have occurred in a given patient.

In making the *lactose test*, 20 grams of milk sugar dissolved in 20 c.c. of distilled water, the solution having been previously Pasteurized at 75 to 80° for four hours on each of three successive days, are injected into a vein at the bend of the elbow; the urine is collected at hourly, or half-hourly, intervals, and tested with Nylander's solution until the reaction for sugar ceases to be positive. The excretion may be followed quantitatively if desired by polarimetry. Normally, all the lactose is excreted in four or five hours. In many cases of renal, disease, the excretion is not completed in seven, nine, twelve, or more hours. The authors assert that, *in such cases of delayed lactose excretion, the renal bloodvessels are diseased.*

In making the *potassium iodide test*, 0.5 gram is given by mouth, and the urine tested every two hours for KI (Sandow's method). Normally, excretion is complete in from 30 to 55 hours. In certain renal diseases, the excretion is prolonged beyond 60 hours, and the authors assert that, *in such cases of delayed KI-excretion, the renal tubules are diseased.*

To determine the presence or absence of an hyposthenuria, and, if present, its type (tubular or vascular), the intake and output of water and of sodium chloride are carefully followed, in the functional testing of Schlayer and Takayasu. They believe that their methods suffice, clinically, to differentiate nephropathies with predominantly tubular lesions from those with predominantly vascular lesions. Thus each nephropathic case is, according to them, to be studied in two directions: (1) as to how KI is excreted (tubular function) and how lactose is excreted (vascular function), and (2) as to how H_2O and NaCl are excreted; if an hyposthenuria be found to exist, one ascertains whether the specific gravity of the hyposthenuric urine is very low (tubular nephropathy), or relatively high (vascular nephropathy), and also if the capacity to eliminate an increased intake of NaCl is lost (tubular disease), or still retained (vascular disease).

The application of these methods is not quite so simple as it sounds, or, rather, considerable caution has to be exercised in interpreting results, owing to certain extrarenal factors which must always be kept in mind. The studies made by Rowntree and his associates indicate that the phenolsulphonephthalein test is a much more reliable indicator of tubular function than the KI test. Schlayer's lactose test may prove to be of very great value.

These studies are all in the right direction, and there is every prospect that functional testing of the kidneys will steadily grow in clinical importance.

SOME THERAPEUTIC PRINCIPLES BASED ON OUR PRESENT KNOWLEDGE OF RENAL DISEASE.

Here, first of all, let me speak of *prophylaxis*. In the nephropathies, perhaps, more than in diseases of other parts of the body, it is easier to ward off a malady than, once it is established, to cure it, What I have said regarding the etiology of the nephropathies gives the clue to the prophylactic measures at our disposal.

To prevent the ascending (urinogenous) nephropathies we try to prevent (1) all obstructions to urinary outflow, and (2) all infections of the urinary passages. When an infection of the lower urinary passages exists, we may try to prevent an ascent (1) by proper treatment of the primary infection, and (2) by copious water-drinking, and the use of hexamethylenamin. In women, some of the infections of the bladder and of the pelvis of the kidney with bacillus coli communis may be due to chronic constipation.

To prevent the descending (hematogenous) nephropathies, we have to learn how toxemias and bacteriemias may be avoided.

Thus, the prophylactic measures to be taken against the toxic tubular nephropathies (sublimate-kidney, chromate-kidney, phosphorus-kidney, etc.) are obvious. How to prevent the pregnancy-nephropathy in the people who are prone to it, we do not yet know, but the knowledge that it is due to absorption from the cavity of the uterus, and that emptying the uterus, in the majority of cases, cures it, stands us in good stead. And since the toxic glomerular nephropathies—the true glomerular nephritides—are often due to streptococcus toxines, the possibility of the complication should be thought of in every case of streptococcus infection. It arises most often after streptoccocus sore throat. Here the general practitioner can do much in the way of prevention. *Every individual who suffers from sore throat, tonsillitis, or a "bad cold" with fever, should be put to bed, and be kept warm there, until the infection is overcome.* Not only would much renal disease be thus avoided, but also many serious diseases of the heart and of the joints. If infections of the tonsils keep recurring, the risk to the kidneys, endocardium, and joints is very great; in many cases, it may be wise completely to excise the infected tonsils. Other foci of chronic infection should be watched for, and, if found, removed (sinusitis; pyorrhea alveolaris; abscesses of the roots of teeth, otitis media; chronic appendicitis; chronic cholecystitis; chronic prostatitis; chronic salpingitis, etc.).

After scarlet fever, patients should be kept in bed for at least four weeks after the onset of the disease, and from the middle of the second week on, the body should be kept warm, and only warm baths should be given, the patient's diet consisting of milk and cereals.

The focal nephropathies, due to bacteriemias, could doubtless often be avoided by preventing, or properly treating, the primary infection preceding a bacteriemia. But we have far to go before we shall learn how to do this in all cases.

Most important at present, perhaps, are our attempts to prevent what I have designated as the arteriolar nephropathy, or genuine contracted kidney due to atherosclerosis of the small arterioles. Prophylaxis here should be directed toward the conditions (toxic) which give rise to the premature atherosclerosis of the arterioles of the organs. Particularly in families in which there is a history of the disease in one, or several, of its members, precautions should be taken early. Over-indulgence in food, especially protein food, in alcohol, in tobacco, and in the pleasures of sex and work may be warned against; if arterial hypertension have already appeared, a strict regime should be instituted and maintained.

In the *treatment* of renal diseases, the dictum of Traube still holds good: "Protect the kidneys and control the heart." In addition to the principle of protection, we can also, at certain stages, successfully apply the principle of exertion to the renal function.

In the protective therapy, we avoid, as far as possible, all further injury to the kidney by intoxication (lead, gout, alcohol, etc.), or infections (chronic tonsillitis, anginas, etc.), and we can lessen, also, the amount of work thrown on the kidney, in normal metabolism, (1) by choosing a suitable diet (limitation of proteins to 100 to 125 grams meat, or its equivalent, of water, to 2 liters, of sodium chloride to 8 to 10 grams and irritating condiments; (2) to a slight extent, by increasing the eliminatory functions of other organs (skin, intestines, lungs); and (3) by lessening the amount of physical or mental work done each day and advising periods of rest, lying down, in the middle of the day. In cases in which the renal disease is compensated, such protective measures are all that is necessary.

To get patients well started on a suitable dietetic regime, the foods should at first be carefully weighed or measured. For this purpose, Dr. C. W. McElfresh, of Baltimore, has found it very helpful to enlist the aid of nurses especially trained in dietetics.

In every case of renal disease, the condition of the heart should be carefully watched. Indeed, chronic passive congestion of the kidneys, due to cardiac insufficiency, may, of itself, cause marked albuminuria and cylindruria. The albumin, as well as the casts, may disappear from the urine when cardiac compensation is reëstablished. And when the kidneys, themselves, are diseased, the urinary symptoms may be markedly exaggerated if the heart begin to fail. "Every renal patient is also a cardiac patient;" in treatment, this should always be kept in mind.

The treatment of cardiac insufficiency, I shall not go into at this

time, as I have already dealt with that topic in a former paper.[11] When the renal disease is not compensated, the kidneys having become insufficient, the rest of the body begins to show certain ill effects, of which the two most important are (1) edema and (2) uremia. In such cases we must make our protective regime still more rigorous, often keeping the patient in bed at complete rest for a time; in addition, we may find it necessary to stimulate renal excretion by diuretics which improve the blood flow through the kidney and excite the renal epithelial cells to increased work.

In combating edema in renal disease, we use diuretics, a salt-poor diet, mild purgatives, and when necessary heart tonics. Diuretin, and the still more powerful theocin, are both excellent stimulants to the renal epithelium, while digitalis preparations improve the circulation in the kidney. In giving diuretin, a dosage of 0.5 gram at 2 P.M. and the same amount at 5 P.M. every other day for a few days may suffice; if not, as much as 4 grams may be given in one day. In giving theocin, 0.1 to 0.2 gram at 10 A.M. and at 4 P.M., every other day for a few days may suffice; if not, as much as 0.8 to 1.0 gram may be given in twenty-four hours. The renal cells may cease to respond; if so, the medication should be stopped, to be tried again a few days later.

Mild purgation is usually sufficient. Violent purgation is often harmful, exhausting the strength of the patient.

The influence of a salt-free (or salt-poor) diet, in reducing renal edema, is sometimes remarkable, especially in acute cases; but a salt-free diet should never be kept up for a long time, or it will do more harm than good. The intake of NaCl may be reduced to 2 or 3 grams per day; in many instances, a reduction to 5 grams per day may suffice. The patient is told to add no salt to his food, and he may use salt-free bread and unsalted butter, together with one liter or one and a half liters of milk.[12] Sugar, rice, potatoes, stewed fruit, fresh green vegetables, salad, chocolate, coffee, tea, and cereals, if no salt be used in their preparation, are practically salt-free foods. Meat and eggs are also salt-free, but should not be used to any great extent, in such cases, on account of their high protein content. In the French clinic of Widal, a salt-poor diet consisting of 200 grams of salt-free bread, 200 grams meat, 250 grams vegetable, 50 grams unsalted butter, and 40 grams sugar is employed. Such a diet contains 1500 calories, and is sufficient for a patient lying in bed. It represents about 60 grams of protein—a low value. I have seen patients, on a similar diet, lose 20 to 30 pounds in a week, from reduction of the edema. The strict salt-free (or salt-poor) diet should not be continued longer than a week at a

[11] On the Treatment of Some of the Forms of Cardiac Failure, Virginia Medical Semi-Monthly, 1911, xv, 457 to 486.

[12] Milk is not salt-free; it contains 1.6 grams of sodium chloride per liter.

time, preferably not over three or four days; then a little more salt (1 to 3 grams) may be permitted, but as far as possible the individual tolerance should be determined, and the patient kept within it. When the patients have a high tolerance for NaCl, there is no good in restricting the salt intake to very small amounts.

In the treatment of uremic symptoms, similar principles are followed, namely, vicarious elimination by mild purgation and diuresis, cardiac tonics, protective diet. When uremia is threatened, it may be well to limit the food, for a short time, to milk sugar, dissolved in water, and fruit juices; later milk may be added. In some cases of uremia, venesection may be life saving; when convulsions recur frequently, lumbar puncture may be tried. In uremic asthma, a small dose of morphine may be necessary. If there be insomnia, or marked nervousness, we may give 0.1 gram of veronal at 2 P.M., at 5 P.M., and at 8 P.M., for a time.

In the management of contracted kidney, we attempt to prevent further action of the cause (atherosclerosis; streptococcus intoxications). To combat a developing atherosclerosis, the whole mode of life has to be systematically ordered. A lacto-vegetarian regime is instituted, and several small meals per day substituted for three large ones. Constipation, if present, is overcome, as is also abnormal intestinal fermentation (administration of Bacillus bulgaricus). The blood pressure should be watched, but it must be borne in mind that the hypertension is a compensatory process, rarely to be combated directly by the high frequency current or by vasodilating drugs (nitroglycerin; sodium nitrite; vasotonin), but, as far as possible, by a prevention of the intoxication which causes it, that is to say, by dietetic and general hygienic measures. Above all, the strength of the heart must be maintained, for unless he die from an apoplexy, the patient suffering from contracted kidney, sooner or later, suffers from cardiac insufficiency. When this begins to appear (dyspnea; cardiac edema), or if uremia be threatened, complete rest and digitalis therapy are indicated; diuresis may be favored by diuretin or theocin, the bowels kept open by mild laxatives, and the skin active by warm packs. Violent sweating is to be avoided.

In contracted kidney, the patients usually pass large quantities of urine. Sudden reduction of the amount is usually a bad sign; it may indicate either a failing heart, or an acute nephropathy, superimposed upon the contracted kidney.

If his life be well regulated, a patient duffering from contraction of the kidneys may go along for many years, even for decades, in comparative comfort, especially if he choose a good climate to live in and avoid infections and chilling of the skin.

THE INFLUENCE OF EXERCISE ON THE HEART.[1]

By R. Tait McKenzie, B.A., M.D.,
PROFESSOR OF PHYSICAL EDUCATION IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

The hour has arrived for a complete reconsideration of the whole question of exercise in relation to the heart.

The invention of new instruments of precision has been followed by the compiling of statistics obtained from observations on the blood pressure, pulse rate, and heart sounds, in normal young people at rest and under exercise; and the frequency of enlargements, variations, and irregularities has been demonstrated, transient or functional in character for the most part, but which might with propriety be termed variations within the normal rather than evidences of a pathological state.

Much medical opinion has of necessity been founded on the evidence of single or occasional cases, or even on that last refuge of the indefinite, "years of experience," which with so many men takes the place of accurate observation, and in consequence children have been classed as diseased or defective and ruthlessly forbidden the exercise and play essential to their physical welfare both present and future. James Mackenzie wisely says, "I have seen numbers of these going through elaborate methods whom I would have sent out to the play fields."

The mere presence of a heart murmur has been considered so serious and disabling in character that the necessary activity of many young people has been harmfully curtailed. Its importance in the field of cardiac symptoms has been grossly exaggerated and too often the more grave and significant signs of heart weakness have been put too far into the background.

As the result of a conversation with Professor Wenckebach, formerly of Groningen now of Strassburg, in which he deplored the lack of accurate information as to the frequency of heart murmurs in different postures of the body and under conditions of rest and exercise in the normal youth, the following observations were taken at the University of Pennsylvania on the incoming class of students whose ages lay between seventeen and twenty-five years:

In common with all well-regulated schools and colleges in America, this university requires a thorough medical examination from all its students on entrance before beginning the course in physical education, which is an integral part of their college work. Out of the thousand and more who came up for this examination in October

[1] Read before the section on Physiology of Exercise, XV International Congress of Hygiene and Demography, Washington, D. C., September 29, 1912.

only those were chosen who presented no apparent defect during the regular medical test. These selected men were given a more careful and thorough heart examination, and when any doubt was felt about the presence of a murmur, two and sometimes three observers made separate examinations.

The selected student took fifty steps of stationary running, raising the knees high at each step so that the heart was brought to a state of great activity. He then lay down on a couch, then sat on a chair, and finally stood up, the stethoscope being applied in each position. For conducting the work and tabulating the results, I am glad to acknowledge with thanks the invaluable assistance of Dr. Ira Ayer. The report includes murmurs only. There were a few cases of arrhythmia or accented aortic or pulmonary second sound without murmur, but these have not been included; nor has note been made of any general conditions like anemia. Such cases were few and the reporter wished to confine himself within the limits of his subject, namely, the frequency with which murmurs develop upon light exercise in individuals in whom no heart lesion is known to exist.

Murmurs that were doubtful have been included, and a few very faint ones that were evanscent were placed in that category. They have been classified according to location under six heads, as follows: (1) apex, (2) apex and base, (3) fourth space just left of sternum, (4) pulmonic, (5) aortic, (6) aortic and pulmonic. They have been classified according to intensity into very faint, faint, moderate, and loud. The quality was in almost every case soft and blowing and puffing, although in a few cases the tone was slightly harsh.

Murmurs were found in 74 out of the 266 men examined (27.8 per cent.), of these 35 were of the pure pulmonic systolic type, and if we include those in which it occurs in combination with others it was present in 64 cases, only 10 men out of 74 failing to show it.

Murmurs were much more frequent in the recumbent position. When they were audible in all three postures they were accentuated when the patient lay down and as the pulse became slower and stronger. This is not to be accounted for by the rotation in which the examinations were made because the order was changed and reëxaminations were frequently made to confirm their result. The following is the table of results:

TABLE OF MURMURS FOUND IN APPARENTLY NORMAL HEALTH AFTER EXERCISE—FIFTY STEPS, STATIONARY, RUNNING.

E = evanescent. B = observed before exercise. V = variable. U = unclassified in strength.

		V. Ft.	Ft.	Mod.	Loud.	Before.	Unclassified.	Total.
Apex	Lying	....	1, E.	1, B.	....	1, B.		
	Standing							
	Sitting							
	L. S. S.	....	1	....	1	....	2	7
Apex and base	Lying	....	1	....	....	1, B.		
	Standing	....	1, E.					
	Sitting							
	L. S. S.	....	....	1	1	3	....	8
Fourth space left of sternum	Lying	2	31, E.	2	....	1	1, V.	
	Standing	....	....	....	....	1		
	Sitting							
	L. S. S.	1	....	3	....	2	1, E.	18
Pulmonic	Lying	1	41, E.	31, E.	....	2		
	Standing	....	....	....	....	2		
	Sitting	2, E.						
	L. S. S.	1	5	3	....	1, E.	9	35
Aortic	Lying							
	Standing							
	Sitting							
	L. S. S.	....	....	1	....	1	....	2
Aortic and pulmonic	Lying	....	....	1				
	Standing	....	....	....	....	1		
	Sitting							
	L. S. S.	....	....	....	....	1	....	3

No marked difference could be found between men who had led an active athletic life and those whose occupation had been sedentary, although murmurs seemed rather to haunt those of inactive habits rather than the more vigorous and athletic. The presence of murmurs in nearly 28 per cent. of normal young men even on slight exertion should, however, lead to caution in giving an unfavorable prognosis when they are found immediately following severe strain or fatigue.

The appearance and disappearance of murmurs by change of posture alone is significant of their unreliability to determine the presence of a real heart lesion when other symptoms are absent.

I have purposely given this investigation in detail because it shows clearly one frequent variation within the normal, and illustrates the fallacy of diagnosticating heart damage from the presence of a murmur only.

Athletic exercise may be divided for our purpose into movements in which a maximum effort or short series of efforts predominate, such as shot-putting, weight-lifting, heavy gymnastics, and sprinting; and movements of endurance in which the single effort is slight but the series prolonged to exhaustion, like walking, cross-country running, cycling.

Exercises of effort produce a sudden and rapid rise in blood pressure to 200 mm. and more, which rapidly falls when the effort is over, the pulse returning quickly to its normal rate. The resili-

ency of the heart and arterial system is tested by such exercises, and they should be avoided by those of advancing years.

Exercises of endurance show a slower rise in pulse rate, and the blood pressure never rises to a great height; but even after the pulse has returned to its normal rate the pressure remains high, returning slowly to the normal. Exhausting tests of endurance, such as take place in long races, are in consequence not adapted to the best development of young and growing children, because of the long-continued period of high blood pressure which they entail. Sudden rise and fall found in exercises of effort have but a minor effect on the elastic vessels of youth.

These two forms of exercise are combined to a high degree in boat-racing. In a four-mile race a series of maximum efforts is continued for twenty minutes; the pulse increases its speed, and the blood pressure rises. The first feeling of exhilaration is replaced by discomfort, followed rapidly by a sense of constriction and pain in the chest and head, anxiety, breathlessness, mental confusion, and in extreme cases by fainting. The oarsman fights desperately for breath, the heart dilates widely as a matter of economy, because every muscle can work better when slightly stretched. This dilatation remains until the equilibrium is reëstablished in the circulation and respiration.

Murmurs always appear and slowly fade away; after the most severe strain one can seldom find any measurable injury in a week's time in a heart originally sound if the athlete has not passed thirty; occasionally, however, they persist longer.

It is in those unprepared for violent exercise, and especially when approaching middle life, that the danger of heart-strain is most imminent.

An ex-football player out of condition suddenly tries to repeat the exploits of his former days; sometimes with alarming results. One, a physician, after such an attempt, writes me as follows: "As we finished I became conscious of a sensation of extreme vertigo in addition to the breathlessness which I had hitherto tried to disregard, and sat down just in time it seemed to prevent falling. The chest appeared full to the bursting point, breathing entirely inadequate, and respiration very rapid. I remember feeling my pulse at the onset of the vertigo and finding it almost indistinguishable. The heart beats soon became strong and almost painful in their intensity, but breathing remained difficult for perhaps half an hour. I sat still for that length of time before I felt equal to walking to the dressing-room, and even then my legs were weak and unsteady. I had marked nausea, but did not vomit. There was a little bloody tinge to the scanty sputa, and several people remarked my pallor. I was uncomfortable and shaky all that evening, but after a night's rest I felt as well as ever, and have so continued."

This is undoubtedly an acute dilatation of a heart on which strain has been put in the unfounded expectation that the resiliency of twenty will be found fifteen years later.

Sometimes an elderly man fresh from his office goes mountain-climbing, and at the end of a hard climb finds himself in such distress as has just been described—a distress which does not disappear when he rests. His heart is found badly dilated and recovery is slow, if it ever takes place completely. Only too often the dilatation remains or recurs on the slightest exertion, and he remains a partial or complete invalid for the rest of his life. Cases are on record of rupture of valves in men aged over forty years, but I have found no record of such a case in the young.

If kept within the limits of overstrain and exhaustion systematic graduated exercise is perhaps the best method of building up the heart in size and strength, and even in most damaged hearts there is no better way of keeping up the tone and efficiency than by movements kept within the limit of fatigue. Stokes pointed this out in Dublin, Oertel in Munich, and it has been confirmed by many others. Controversy has raged fiercely, however, over the remote effects of the more active and violent exercises and sports, and too often opinion, prejudice for or against, or vague impression has taken the place of the observation of facts.

The only statistics on which reliance can be placed show the following results:

E. H. Morgan in his report on 294 old oarsmen found an increase of two years in their expectation of life over the selected lives of Farr's English Life Tables.

George L. Meylan in his report on 152 Harvard oarsmen found an increase of 1.6 years, but his results were interfered with by 8 deaths in battle during the Civil War. Allowing them their allotted span, the expectation would show an increase of 5.39 over the selected lives of actuarial tables.

W. G. Anderson found that the graduates of Yale who had won their "Y" on athletic teams showed a mortality considerably less than that of all other graduates.

Dr. Armstrong, of Wellington College, in 198 cross-country and steeplechase runners finds of the 13 deaths from 1870 to 1904 that none died from heart conditions.

Hammett in his exhaustive compilation of distance runners found similar results.

Blake and Larabee, in speaking of Marathon runners, after that most exhausting of all athletic tests, write: "So far as observed no permanent injury of any kind has resulted from participation in these races."

Baruch and Savage, in their most exhaustive and painstaking observation on Marathon runners, come to much the same conclusion, although with more reservation.

It may be taken as demonstrated, then, that even severe athletic competition does not, as a rule, appreciably damage the circulatory apparatus, and its role in hastening the onset of arteriosclerosis is still difficult to determine. Certainly it is not to athletics, but to the much more strenuous occupations continued throughout long hours and under unsanitary conditions, as coal-mining and iron-working, that one must look for information on this subject.

The exhaustion of continual overstrain in the young and growing would of necessity be unfavorable to the child's best interest, but even in them the recovery is so rapid and complete that one is astonished at its thoroughness.

The body is constructed for a life of physical activity and the heart needs constant and varied movement for its proper development. Anything which curtails or prevents this natural means of growth must result in preventing the individual from reaching his highest possibilities.

OBSERVATIONS ON A CASE OF MEDIASTINOPERICARDITIS TREATED BY CARDIOLYSIS (BRAUER).

By Arthur D. Dunn, M.D.,

PROFESSOR OF MEDICINE IN THE JOHN A. CREIGHTON MEDICAL COLLEGE, OMAHA,

AND

John E. Summers, M.D.,

OMAHA, NEBRASKA.

History: J. F., aged twenty-nine years, consulted one of us February 5, 1912. He is single and is a florist by occupation. Formerly he was a steady drinker but during the last two years he has drunk almost none. It is to be noted that the *only illness he has suffered during his entire life was diphtheria followed by "paralysis" at eleven.* The family history is negative.

The present illness began gradually three years ago with "bloating," with tiring easily, and with shortness of breath on exertion. His condition grew rapidly worse and almost from the beginning he has been entirely incapacitated. He says he cannot lie down without several pillows and he spends his nights largely in a chair; he cannot move about without choking and coughing; he is able to eat but little and his abdomen is bloated so that he cannot button his trousers; his bowels will not move without medicine; his urine is scanty and highly colored; he has had much yellowish sputum in which there has occasionally been considerable amounts of blood.

Status Præsens: The patient is a well-developed young man.

Dyspnea and orthopnea are marked. His face is a dusky red, the veins of his neck and face are turgid and a marked venous diastolic collapse is present. In the precordium a violent pulsation is to be seen which consists of a distinct rather slow systolic retraction with a rapid vibratory diastolic thrust. There is a systolic retraction of the left costal arch. Broadbent's sign is present. The respiration is rapid and upper thoracic in type. A marked diastolic shock can be palpated. The apex lies in the sixth interspace in the anterior axillary line. Cardiac dulness extends 3 cm. to the right of the sternum, and to the left as far as the anterior axillary line in the sixth interspace. The area of heart dulness does not change with change of position. Auscultation reveals a loud systolic murmur heard over the entire precordium; this murmur is best heard at the apex. All of the sounds are blurred, the heart action is rapid (120 per minute) and irregular. A second diastolic heart sound can be heard over the entire right ventricle.

There is an obliteration of the left lower pleural cavity. The lower border of the left lung in the precordium does not move with respiration. The right cavity contains a moderate amount of fluid.

The abdomen is much distended. The liver extends a hand's breadth below the costal arch in the nipple line; it is tender and pulsates. Ascites is present. The scrotum, thighs, legs, and feet are moderately edematous.

The urine is highly colored and sharply acid, the sp. gr. is 1030. Albumin and the aldehyde reaction are present; sugar is absent. Hyaline and granular casts and red blood cells are numerous.

The patient was placed in the hospital, where in the course of three weeks, compensation was restored; the heart action became regular, the murmur entirely disappeared, and the heart sounds became clear. The patient's temperature was normal during the entire time.

Ten days later (March 13, 1912) cardiolysis was performed by Dr. J. E. Summers. The purpose of the operation was not only to untether the heart by doing away with the costopericardial adhesions, but also to give the enlarged organ room for freer play.

A U-shaped incision, commencing four inches from the sternum, was made, with its base directed toward the left shoulder, the upper limb skirting the lower border of the second rib as far as the sternum, thence the curved portion overlapping the left border of the sternum to the cartilage of the sixth rib, the lower limb continuing downward, outward, and then upward to the anterior axillary line (Fig. 1). A musculacutaneous flap down to the ribs was raised, and the third, fourth, fifth, and sixth ribs and their cartilages covered by their periosteum and perichondrium were resected flush with the sternum. This exposed the pericardium

and left pleura in an area measuring from above down, five inches: from within, out, four and one-half inches.

The pericardium was found adherent to the chest wall and the pleura somewhat thickened and adherent. It was not necessary to ligate the internal mammary artery, as the costal cartilages were first divided externally to the course of this vessel and then the inner stumps were removed. The wound was closed with a cigarette drain in its lower inner angle, which was taken out at the end of twenty-four hours. The operation was followed by a mild bronchopneumonia, from which the patient's compensation was little disturbed. In other respects convalescence was uneventful.

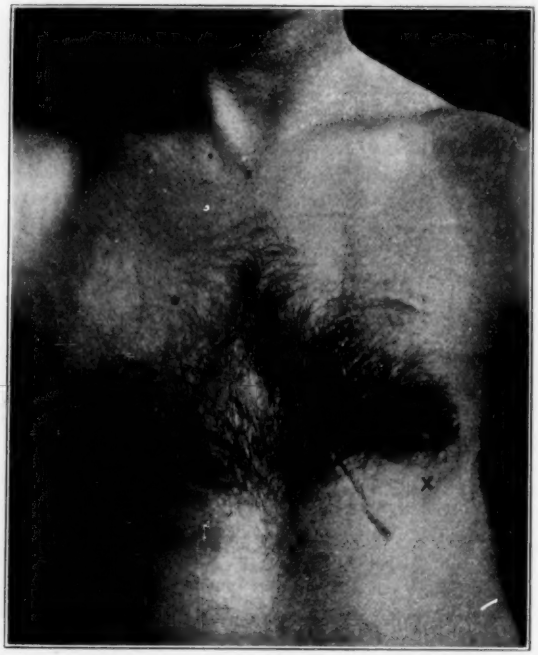


FIG. 1.—Photograph taken three months after operation, showing incision. The blurring at the apex indicates the freedom of the movement of the heart. (Time exposure.)

The following interesting etiological and pathogenic feature was to be noted in our case. The onset was insidious, and except for diphtheria, when aged eleven years, there had been no definite infection or illness to which the condition could be attributed. The beginning of symptoms in early manhood, at that period in which the chest wall "stiffens," argued that the adherent pericarditis had come down from childhood. As costochondral ossifica-

tion advanced during adolescence, there was an ever-increasing demand for power to mobilize the precordium. The obliteration of the left pleural cavity was significant of a snychronous pleurisy. A chronic adhesive pleurisy, as is well known, becomes a factor of no little importance in a circulatory problem, in which the work to be done approximates the power available. The effect is on the right ventricle, which is always most at a mechanical disadvantage in mediastinopericarditis. The clinical picture pointed chiefly to interference with the action of the right ventricle, and it was clear that in such a condition much was to be expected from cardiolysis.

At Brauer's[1] instigation the first operation for adhesive mediastinopericarditis was performed by Peterson in 1902. Brauer termde the operation cardiolysis, because it loosened the heart from its harness. Since then the operation has been performed some thirty times, with results which depended to a large extent upon the judgment with which the cases were selected. P. Lecène,[2] from his analysis of 20 cases, states: "The operative mortality of this intervention has been nothing to date. And truly one should not be surprised at this, since on the whole it is only a question of a small operation of general surgery. The anesthesia alone could be dangerous; it is sufficient to watch the anesthetic carefully and reduce it to the minimum." This Gallic surgical optimism is not to be taken too seriously. The dangers of the procedure should not be minimized. Operative mortality should be held to include cardiac deaths occurring in the first days following operation; more deaths have probably occurred than have been recorded.

Brauer postulated that for the success of the operation the following conditions must be present: *diastolic shock, systolic retraction at the apex, and the ability of the heart muscle to compensate.* If from myofibrosis, mycardial degeneration, or from valvular disease the heart is unable to compensate, the operation will be futile. Today we must consider also as generally contraindicated those cases in which the pericarditis is part of a tuberculousis; all such cases in which operative interference has been tried have been benefited little. If the pericarditis is part of a general polyserositis, the results will be bad. Schlayer[3] justly maintains that the results of cardiolysis do not depend alone on the condition of the heart. Attention must be given to the serous membranes. In 10 out of 12 cases of his series one and frequently both pleuræ were involved. He believes that the pleuræ in mediastinopericarditis show an extraordinary tendency toward inflammatory processes, and that the processes are by no means transitory, but make for recurrence in the majority of cases. The ascites present must not be considered to be secondary in all cases to cardiac impairment.

[1] Münch. med. Woch., 1902, xlix, 982; Arch. f. klin. Chir., 1903, lxxi, 258.
[2] Arch. des Maladies du cœur, de Vaisseaux et du Sang.
[3] Ueber adhäsive Pericard-obliteration u. Kardiolyse, Münch. med. Woch., 1910, lvii, 729.

If the ascites disappears, with the restoration of compensation, it is probably of cardiac origin; if it does not, it is dependent on a co-existent inflammatory condition of the peritoneum. Schlayer considers two types of mediastinopericarditis: the cardiac and the polyserositic. Anatomically, and to a lesser extent clinically pericarditis may be divided into the following types: diaphragmatic, pleural, chondrocostal, and mediastinopericarditic. The cases may be said almost never to be of a pure type. The existence of the chondrocostal type is necessary if we are to expect anything from operative interference. The heart is hitched fore and aft to the chest wall and to the vertebral column by involvement of the pleura, pericardium, and posterior mediastinum. It is at this double pull that our therapy is directed. An additional indication for rib removal in cardiac disease has been advanced by Alexander Morrison.[4] In a patient with cor bovinum from mitral and aortic disease who suffered from frequent and severe "anginoid" pains that resisted treatment, he removed $4\frac{1}{2}$ inches and $5\frac{1}{2}$ inches of the fifth and sixth ribs respectively. The result was subjectively and objectively gratifying, so that the patient was able to earn his living, which he had previously been unable to do. He was reported much improved one and one-half years after the operation. Morrison's reasoning was as follows: Experiments show that direct muscle stimulation of the eviscerated heart induces contraction. (One of us has been able to induce contraction in the exposed heart of a five-months-old fetus, four hours after birth, by lightly tapping the right ventricle with a thumb forceps.) The constant thumping of the heart against the stiff and confining chest wall gives rise to a cardiac erythism. Morrison believes that one of the causes of pain and increased irritability in greatly hypertrophied hearts is this impact of the forcefully beating heart on the chest wall. The substitution of a soft tissue covering for the heart instead of a bony wall admits of free action of the hypertrophied heart without the constant hammering of the chest wall. The free play afforded the greatly hypertrophied and dilated heart by the operation was noticeable in our case. The correctness of Morrison's reasoning must be determined by extensive clinical application of this theory. We would suggest the term *cardiac decompression* in place of thoracostomy, as used by Morrison, because it better describes the purport of the operation.

Tracings made from our patient before and after operation show some interesting features:

Sphygmogram (Figs. 2 and 3): Before the operation the radial pulse was of such poor volume that an adequate sphygmogram was difficult to obtain. During inspiration the pulse was more rapid, and showed less volume—the pulsus paradoxus of Kussmaul.

[4] Lancet, July 4, 1908; November 20, 1909.

This latter condition has not been materially affected by the operation, but the pulse volume has been much improved. (Vide tracings and legends.)

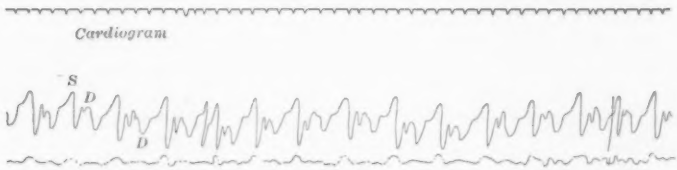


FIG. 2.—Tracing taken at the apex and from the radial pulse two days before operation. *S*, systolic wave; *D*, diastolic wave. Note wave in the diastolic phase of the sphygmogram.

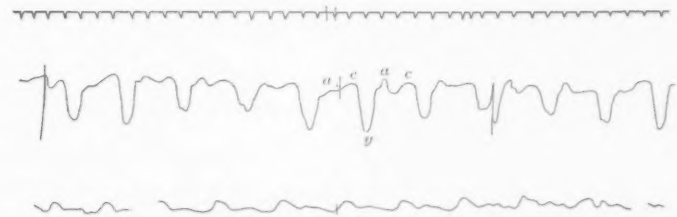


FIG. 3.—Tracing taken from the left jugular vein and from the radial pulse two days before operation. *a*, auricular wave; *c*, carotid wave: *y*, diastolic phase.

Cardiogram: The cardiogram before the operation showed a distinct wave (*D*) in diastole (Fig. 2). This wave was the most marked feature of the cardiogram. Its counterpart can also be seen in the radial tracing; it was synchronous with the diastolic shock. We are at a loss to explain the two wavelets on the crest of the diastolic wave, unless it be a graphic representation of a distinct diastolic vibration, which was palpable, and which was probably due to the resilience of the chest wall. In the systole (*S*) of the cardiogram there is a marked hesitation on the contraction, then completion of the systolic wave followed by a sudden diastolic phase. This feature is not present in the cardiogram taken directly from the apex after the operation. This marked hesitation in the upstroke can be explained by the sudden bringing up of the muscle by the resistance of the surrounding structures which must be mobilized suring each systole.

Phlebogram (Fig. 3): The venous pulse taken before operation *after compensation has been restored*, showed a prolonged *a–c* interval and a marked diastolic negative phase (*y*). The shortening of the *a–c* interval and the marked diminution of the diastolic wave (Figs. 4, 5, and 6). After the "untethering" of the right ventricle is a graphic demonstration of the therapeutic value of the opera-

tion. It must be remembered that our control tracing was taken after compensation had been brought about by three weeks in bed and ten days up and about the hospital at comparative rest. Digitalis had not been used for over four weeks before Fig. 3 was taken.

Fig. 4 is from a tracing taken two weeks after the operation. Already the diastolic negative phase is decreased. The tracing of April 9, four weeks after the operation shows still less of the negative phase *y* (Fig. 5). The phlebogram taken April 22, about six weeks after the operation, shows a normal phase *y* (Fig. 6).

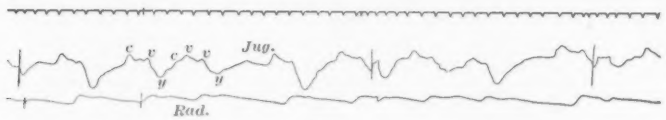


FIG. 4

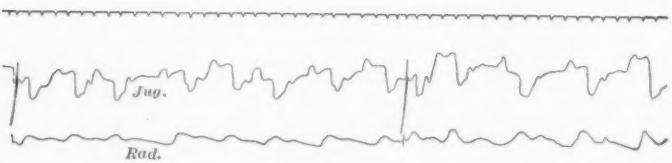


FIG. 5

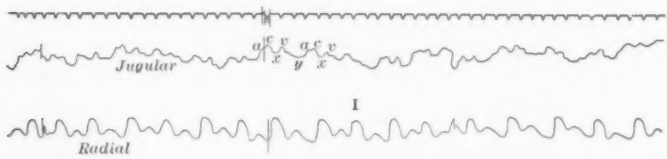


FIG. 6

FIGS. 4, 5, and 6.—Phlebograms taken two weeks, four weeks, and six weeks after operation. Note the shortening of the *a–c* interval, the progressive diminution of the negative phase *y*, and the appearance of a first negative phase with its corresponding wave *x* separating it from the negative phase *y* in Fig. 6. In the tracing before operation only one negative phase was present;

Brauer's work has changed the diagnosis of adhesive pericarditis from an academic problem into one with a practical therapeutic corollary. The systolic retraction at the apex, the diastolic shock, epigastric diaphragmatic tugging, Broadbent's sign, and cardiac and pulmonary immobility are well known and do not require

discussion here. Pick's pseudo-cirrhosis of the liver gives us a clinical picture which varies from the typical pericarditis. Insidious onset, ascites which rapidly recurs after puncture, intermissions and remission with signs of involvement of the pericardium, characterize the condition. There are two varieties of the disease described. In one type, the true Pick's pseudo-cirrhosis of the liver, the adhesive pericarditis appears to be the causative lesion, the result of which is a chronic stasis of the liver and portal systems, and the formation of an indurative (cirrhotic) nutmeg liver. *The pericarditis* may be well concealed by the other more apparent manifestations. In the polyserositic type we find the iced liver (Zuckergussleber), in which there is a distinct chronic peritonitis.

FIG. 7.—Tracing taken from the exposed auricle and from the apex two weeks after operation.

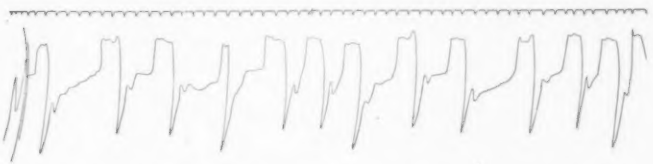


FIG. 8.—Tracing taken direct from the apex three weeks after operation.

In the former class operation is indicated, but where there is evidence of extensive chronic peritoneal inflammation, surgery is contraindicated as far as the mediastinoperocarditis is concerned. Our case partook somewhat of the true Pick's cirrhosis type. There was a large ascites with relatively less edema of the feet. The liver was large and hard, and did not regain its normal size until three weeks after the operation. The disproportion of liver and portal stasis to stasis elsewhere was also true of Wenckebach's case.

It is well briefly to review some of the patholigcal physiology of adhesive mediastinopericarditis. In normal respiration, as the diaphragm moves downward, the abdominal contents are carried downward and forward following the descent of the diaphragm. During expiration the contents move upward and backward. This downward movement of the diaphragm presses the blood out of the liver like squeezing a sponge. The heart moves up and down with the excursion of the diaphragm; in the words of Keith: "The lungs carry their pump with them." According to Wenckebach,

the following disturbed functions result in mediastionpericarditis: (1) The descent of the diaphragm is markedly inhibited. (2) During inspiration the diaphragm pulls at the heart and *via* the heart at the chest wall, at the root of the lungs and at the posterior mediastinum. (3) The heart and large vessels being fixed to their surroundings, inspiration produces a worse condition than expiration. (4) Respiration becomes defective in all of its factors. Deficient movement of the diaphragm and impediment to inspiratory action due to anchoring of the diaphragm results. In this connection Wenckebach[5] emphasizes the absence of forward movement of the chest as an important diagnostic sign of adherent pericarditis. This author believes that the process of respiration profits by the operation much more than the heart action. In our case the deficient movement of the chest in respiration was striking. The epigastrium seemed to be sucked in with inspiration rather than protruded, and the anteroposterior excursion of the chest wall was slight.

The scope of this paper is too limited to take up in detail the numerous interesting phenomena incident to adherent pericardium. We have purposely avoided the complex problem of diagnosis, for which the literature seems adequate. We wish merely to call the attention of American physicians and surgeons to the procedure by reporting a case in which the result to date (December 1, 1912) has justified operative intervention.

A fairly comprehensive view of the subject may be obtained by consulting the following bibliography:

Schwarzenauer. Pericardio-Mediastinalen Verwachsungen u. Cardiolyse, 1907.

Glück. Zur Chir. des Herzbeutels, Arch. f. klin. Chir., 1907, lxxxiii, 1612.

Venus. Die Operative Behandlung der Pericarditis, Wien. kl. Rundschau, 1908, xxii, 695 to 711.

Urban. Ueber Kardiolyse bei Pericardio-Mediastinalen Verwachsungen, Wien. med. Woch., 1908, lviii, 391–399.

Poynton and Trotter. A Case of Cardiolysis, Proc. Roy. Soc. Med., London, 1909–10, iii, Chirurgical Section, 199.

Roux-Berger. Le Traitement Chirurgical de la Mediastino-pericardite adhesive, Semaine Méd., 1910, xxx, 423 to 426

Sinnhuber. Die Erkrankungen des Herzbeutels u. ihre Behandlung, Berlin, 1911.

Wenckebach, K. F. Beobachtungen bei exsudativer u. adhasiver Pericarditis, Zeitsch. f. allg. Med., 1910, lxxi, 402 to 420.

Sutherland, G. A Case of Cardiolysis for Adherent Pericardium, Proc. Roy. Soc. Med., London, 1910–1911, Medical Section, pp. 40 to 50.

[5] British Med. Jour., 1907, i, 63.

THE RELATION OF PARASITIC AMŒBÆ TO DISEASE.[1]

By Charles F. Craig, M.D.,
CAPTAIN, MEDICAL CORPS, U. S. A., WASHINGTON, D. C.

(From the Bacteriological Laboratory of the Army Medical School, Washington, D. C.)

Introduction. Within the last seven years it has been definitely proved that the parasitic amœbæ of man, or entamœbæ, are divided into several distinct species, one of which is a harmless commensal; that all cultural amœbæ which have been thoroughly studied are free-living species having nothing in common with the parasitic species, and that the latter have not been cultivated.

These new developments in our knowledge of amœbæ necessitates a revision of some of our data connecting these organisms with disease in man, for all of the evidence gained by experiments on animals or man with cultural amœbæ must be discarded, as such evidence is of no value as showing the relation of parasitic amœbæ to disease in the human subject. In addition, the results obtained experimentally in animals by feeding or injecting material containing entamœbæ must be revised in the light of the proved existence of a harmless and at least two pathogenic species.

Classification of Amœbæ. In considering the relation of entamœbæ to disease in man it is necessary to have a clear understanding of the classification of amœbæ in general. Loesch placed the amœba he found in man in the genus *Amœba*, calling it *Amœba coli;* in 1879, or four years after the discovery of *Amœba coli*, Leidy established the genus *Endamœba* for the parasitic amœba of the cockroach, described by Butschli under the name *Amœba blattæ;* in 1897, Casagrandi and Barbagallo, after a thorough study of the amœbæ occurring in the intestine of man, became convinced that they differed both in morphology and life cycle from those occurring free in nature, and, apparently unaware of Leidy's genus *Endamœba*, established for the human parasites the genus *Entamœba*. While eventually it may be determined that the spelling of Leidy must be retained, I prefer at the present time to accept the name *Entamœba* for the parasitic amœbæ, as this term has been accepted and is used by almost every writer upon the subject.

After the researches of Casagrandi and Barbagallo, numerous attempts were made to separate the entamœbæ into distinct species, but it was not until 1903 that a clear description was given of at least two species of entamœba occurring in man. During that year, Schaudinn published his work upon parasitic amœbæ, and

[1] Published with permission of the Surgeon-General of the United States Army. Read before the XV International Congress of Hygiene and Demography, Washington, D. C., September, 1912.

differentiated two species: One, a harmless parasite, which he named *Entamœba coli;* the other, the cause of a form of dysentery, which he named *Entamœba histolytica.* I was able to confirm Schaudinn's work in 1905, and it has since been confirmed by many protozoölogists in various parts of the world. Recently Prowazek found this species in dysentery cases in Samoa, and states that at no time in its cycle of development were cysts observed at all resembling those found in other parasitic species, but only the spore-like bodies described by Schaudinn.

A third species of entamœba was described by Viereck in 1906. This parasite, which he named *Entamœba tetragena,* occurred in cases of dysentery contracted in Africa, and his researches, as well as those of others, proved it to be a pathogenic species, and that it has a wide geographical distribution in the tropics and subtropics, as well as in temperate climates. I have found this species in cases of dysentery contracted in the Philippines, Panama, and in New York, Illinois, Arkansas, and Wisconsin. At the present time some authorities believe that this species is identical with *Entamœba histolytica,* but the point is far from proved, and until it can be shown that the process of reproduction by gemmation and spore-formation, described by Schaudinn as characteristic of *Entamœba histolytica,* and confirmed by myself in many cases of dysentery, occurs also in *Entamœba tetragena,* and that cases of *tetragena* infection occur which never present the characteristic four-nucleated cyst at any stage of the disease process, I am forced to consider the two species as distinct, despite the fact that the nuclear structure of *Entamœba tetragena,* during certain stages of development, resembles very closely that of *Entamœba histolytica.*

In addition to the three species mentioned, several others have been described in man, as *Entamœba tropicalis,* Lesage; *Entamœba minuta,* Elmassian; *Entamœba nipponica,* Koidzumi; *Entamœba williamsi,* Prowazek; *Entamœba hartmanni,* Prowazek; and *Entamœba polecki,* Prowazek. It is generally believed that most, if not all, of these species are founded upon insufficient data, and that eventually they will be found to be identical with one or the other of the three species already mentioned.

It may, therefore, be stated that at the present time most authorities recognize three distinct species of entamœba as parasitic in man, that is, *Entamœba coli, Entamœba histolytica,* and *Entamœba tetragena.* These species have been carefully studied by numerous investigators in many parts of the world, and are based upon marked differences in morphology and in the reproductive cycle. The nuclear structure of each species is distinctive, while *Entamœba coli* forms cysts containing eight daughter nuclei, this number being sometimes exceeded: *Entamœba tetragena,* cysts containing four daughter nuclei; and *Entamœba histolytica,* cyst-like bodies, which are budded from the parent organism. In all these species

the differences in the method of reproduction have been carefully studied, and, in my opinion, constitute the most important basis of specific differentiation.

The classification of the amœbæ that have been cultivated from the feces of dysenteric patients and from the pus of liver abscesses is in a most unsatisfactory condition. Several species and subspecies have been described by Whitmore, Walker, Williams, Werner, and others, but no agreement has been reached as to their exact specific status. For long regarded by Musgrave and Clegg, Walker, La Sage, and Noc as true parasitic species, identical with the species of entamœba which have already been mentioned, these cultivated amœbæ have been shown to be free-living species of the *limax* type by the more recent work of Hartmann, Werner, Whitmore, Walker, Liston and Martin, Wells, and the writer. All the cultural species that have been thoroughly studied contain a contractile vacuole, an organelle which is not present in any of the parasitic species of man, and they also differ greatly in their reproductive cycle. This subject will be referred to later in the discussion of the relation of these cultural species to disease.

Relation of Entamœbæ to Disease. The following theories have been held regarding the relation of entamœbæ to disease in man: (1) That they are all harmless commensals; (2) that they are secondary factors in the etiology of disease; (3) that all species of amœba are capable of causing dysentery, and (4) that both pathogenic and non-pathogenic species are parasitic in man.

Recent researches have shown that the latter theory, that is, that pathogenic and non-pathogenic species of entamœba are parasitic in man, is correct. It is still impossible to say whether some other factor is necessary before the pathogenic species can cause disease, but the evidence all points to the contrary opinion. At the present time it is generally accepted that certain species of entamœbæ are capable of producing dysentery, but a few authorities still maintain that these parasites are only secondary invaders of the tissues, and are not responsible for the lesions present. In support of this contention they point to the fact that entamœbæ are found in many healthy individuals and in patients suffering from diseases other than dysentery; that dysentery occurs in epidemic and endemic form in regions where entamœbæ cannot be demonstrated; that many different agents when injected into the intestine are capable of producing lesions like those of amœbic dysentery; that direct infection of either animals or man with entamœbæ has never been proved; that the deductions based upon animal experiments are unsatisfactory, and that until we are able to cultivate the entamœbæ and to produce dysentery with pure cultures we are not justified in claiming that they are the cause of the disease.

These objections, with the exception of the last mentioned,

can all be answered by the results of work accomplished during the last few years. We know that the presence of entamœbæ in health and in diseases other than dysentery is explained by the occurrence of a distinct species which is non-pathogenic and which is a parasite of man; that the occurrence of endemic and epidemic dysentery in regions where entamœbæ have not been demonstrated is due to the group of dysentery bacilli; that the lesions produced by the injection of either chemical or bacterial substances into the intestine are *not* identical with those produced by the entamœbæ; that direct infection of animals with entamœbæ has been abundantly proved, and that such experiments *are* reliable when properly controlled. As regards the last objection, that is, that until pure cultures are obtained the causative relation of entamœbæ to disease cannot be maintained, it may be stated that this is not a fair or valid objection, as there are other parasites well known to be the cause of specific infections which have not as yet been cultivated.

In support of the etiological relation of certain species of entamœbæ to dysentery we have the following facts: (1) The absolutely characteristic pathology of amœbic dysentery and the constant presence of the pathogenic species of entamœba in the lesions and their absence from the lesions of other forms of dysentery; (2) the constant presence of pathogenic entamœbæ in the tissues of the peculiar form of liver abscess which often complicates amœbic dysentery; (3) the production of typical amœbic dysentery in susceptible animals by feeding and inoculation experiments with material containing the pathogenic entamœbæ and the demonstration of the parasites in the lesions so produced.

It is not necessary at this time to discuss in detail the pathology of amœbic infection. It is a self-evident fact to all who have had experience with amœbic dysentery at the autopsy table that the lesions of this disease are absolutely characteristic and are entirely distinct from those of the bacillary forms of the disease. I have had the opportunity of studying hundreds of cases of both amœbic and bacillary dysentery at autopsy, and can state that one may easily distinguish the lesions produced by the entamœbæ from those due to other causes.

If sections are made through the lesions in the intestine, entamœbæ may be demonstrated in every portion of the involved region. They are frequently numerous in the mucous, submucous, and muscular coats of the intestine, where they may be demonstrated in the glandular tissue, in the intermuscular septa, and in the lymphatics and bloodvessels. Of course, in the intestine it cannot be denied that a portion of the pathological picture may be due to bacteria which have gained entrance to the tissues along with the entamœbæ, but the fact remains that the latter organisms are always associated with a characteristic ulcerative lesion never produced by bacteria alone.

I believe that if we had no other evidence than the peculiar lesions of this form of dysentery with which are always associated the pathogenic species of entamœba we would be justified in considering the latter as the cause of the disease.

It is well known that a peculiar form of liver abscess frequently complicates amœbic dysentery. The pathology of this condition is characteristic, and in the contents of such abscesses entamœbæ can always be demonstrated, and if sections are made of the abscess wall these organisms are found within the tissues. Frequently the abscess contents are sterile save for the entamœbæ, while the most careful staining of the tissues fails to reveal any other etiological factor.

The experimental production of dysentery in susceptible animals with entamœbæ dates back practically to the discovery of these parasites. Loesch produced the disease in a dog by the rectal injection of fecal material containing entamœbæ, and his results were confirmed upon cats by Hlava, Kovacs, Kartulis, Zancoral, Strong and Musgrave, and many others. Huber produced dysentery in dogs by feeding them feces containing entamœbæ, and Kruse and Pasqualle produced the disease in cats with the pus from an amœbic liver abscess. The work of Harris, which has been largely overlooked by writers dealing with this question, was of great interest and importance. He endeavored to produce dysentery in dogs by the rectal injection of various bacteria and fecal material from dysentery cases. Among the bacteria injected were the typhoid bacillus, colon bacilli, anthrax bacilli, pyogenic cocci, the dysentery bacillus of Shiga, and mixed cultures of bacteria from dysentery patients. His experiments were most carefully controlled, and in not a single instance did the animals show any evidence of disease following the injection of the bacteria. On the other hand, the injection of fresh feces containing entamœbæ, in the rectum of puppies, was followed in every case by a typical dysentery resulting in the death of the animal experimented upon. In two of the animals amœbic abscess of the liver developed and entamœbæ were recovered from the abscess pus. In all of the animals, four in number, the lesions present in the intestine were typical of those found in amœbic dysentery in man. The period of incubation varied from three to six days. Sections of the intestine of the infected animals exhibited the microscopic pathology of amœbic dysentery, and the entamœbæ were demonstrated in the tissues.

All the experimental work cited, while conclusive as to the production of dysentery in susceptible animals with material containing entamœbæ, is inconclusive as regards the exact species used in the experiments, as these researches were made before Schaudinn's work in species differentiation. Since his observations, however, numerous investigators have proved that

Entamœbæ coli is not a pathogenic organism, and that *Entamœbæ histolytica* and *Entamœbæ tetragena* are the species most frequently concerned in the etiology of amœbic dysentery.

Relation of Entamœbæ Coli to Disease. *Entamœbæ coli* is a species frequently observed in the feces in both health and disease. Although it is probably world-wide in its geographical distribution the percentage of infection varies greatly in different localities, being highest in tropical countries and lowest in cold climates.

Schaudinn found it present in 50 per cent. of healthy individuals in West Prussia; in 20 per cent. in Berlin, and 66 per cent. of healthy people examined on the shores of the Adriatic Sea; Vedder, in 50 per cent. of healthy American soldiers, and 72 per cent. of Filipino scouts in the Philippines; Sistrunk, in 11 of 145 patients suffering from diseases other than dysentery in the Mayo Hospital at Rochester, Minnesota, the patients coming from different parts of the United States; and Ashburn and the writer in 71 per cent. of healthy American soldiers in Manila. In 1905, I examined over 200 American soldiers in San Francisco, who were recruited from different parts of the United States, and found that 65 per cent. of them showed *Entamœba coli* in the stools after a saline cathartic. This species has lately been demonstrated by Stiles in North Carolina, by McCarrison in India, and its occurrence in the Philippines confirmed by Whitmore and Walker. It has also been found upon the Isthmus of Panama by Darling and James, in South America by Elmassian, and in Samoa by v. Prowazek.

That this organism is not pathogenic has been proved by many investigators. Its common occurrence in healthy individuals, in whom it has been observed for months and even years without producing symptoms of diarrhea or dysentery, and the negative result of animal experiments by numerous investigators proves that this species is a harmless commensal of the human intestine. Negative results were obtained by Kartulis, Kruse and Pasquale, Celli and Fiocca, Strong and Musgrave, Kovacs, and Jürgens by injecting material containing entamœbæ parasitic in healthy individuals, and Schaudinn showed that this entamœba, which he called *Entamœba coli*, is capable of living in the intestine, but that it never produces symptoms of diarrhea or dysentery either in animals or man.

I have made many attempts to produce dysentery in kittens with *Entamœba coli*, both by injecting fecal material containing them into the rectum, and by feeding material containing both the encysted and vegetative forms, but have never been able to produce the least symptom of dysentery, although 50 per cent. of the kittens given rectal injections of feces containing *Entamœba histolytica* and 65 per cent. of kittens fed with milk infected with material containing the same species developed severe dysentery.

In a recent personal communication Doctor Creighton Wellman

has furnished me with some data regarding experiments with *Entamœba coli*. He infected five kittens by injecting 4 to 5 c.c. of feces containing encysted *Entamœba coli* into the rectum. All the animals remained perfectly well, and were killed about one month after the injection. In none of them were any evidences of dysenteric lesions found at autopsy.

From the evidence which has accumulated it may be positively stated that *Entamœba coli* is not a pathogenic parasite, and that it has been found in a considerable proportion of healthy individuals in every region where it has been carefully searched for. This parasite is chiefly of importance because of the liability of confusing it with the pathogenic entamœbæ, and there can be no question that hundreds of cases of so-called amœbic dysentery have really been diarrheas due to other causes, but so diagnosticated because of the finding of *Entamœba coli* in the stools.

Relation of Entamœba Histolytica to Disease. I have already mentioned the numerous instances of the production of dysentery with material containing entamœbæ, but Schaudinn was the first to demonstrate the actual species concerned in many of these experiments. This species he named *Entamœba histolytica*, and he conclusively proved that it is the cause of a form of dysentery, and that the so-called spores of this parasite are infective. He thus describes his experiments which prove this point:

"From this case I took a small quantity of feces, divided it into three parts, dried each in the air, and mixed with it sufficient water for about twenty crush preparations under cover-glasses. These preparations were carefully examined, the examination being conducted upon a mechanical stage, and requiring many hours. No forms resembling the cysts of *Entamœba coli* were found, but the small spores of *Entamœba histolytica* were noticed in large numbers, but no vegetative organisms could be demonstrated. The cover-glasses were then removed, the feces washed with distilled water, and ten such preparations were mixed with enough distilled water to form 1 c.c. of the mixture. The feces of the animal to be experimented upon, a healthy, strong, young cat, was carefully examined for amœbæ, and none could be demonstrated. To this cat I gave the 1 c.c. preparation mentioned above, mixing it with milk. On the evening of the third day the cat passed bloody mucoid feces, and an examination showed the presence of great numbers of typical *Entamœbæ histolytica*. In the afternoon of the fourth day the cat perished. Dissection showed typical ulcerous dysentery of the large intestine, and immigration of the amœbæ into the epithelium could be easily established.

"I will mention yet another experiment which goes to prove that the permanent spores by themselves are capable of producing a new infection. The feces of the cats developing dysentery contained only vegetative stages of the amœbæ, no spores being

found. When large quantities of the feces were given to a cat it remained well and for four weeks showed no amœbæ in its feces. It was then fed with the remnant of the dried feces used in the first experiment, which contained multitudes of the spores, and after six days the amœbæ began to appear in the feces. Being older and larger than the other cat it proved more resistant to the infection and did not die until two weeks later. The autopsy showed the lesions of typical amœbic dysentery."

Schaudinn's work served to explain the negative results of some observers with *Entamœba histolytica*. During the active stage of dysentery only the vegetative forms of this species occur in the feces, and as these forms are not infective by feeding, the experiments in which only material containing these forms are used will give negative results. However, if the feces from cases which are recovering from dysentery are used for experimental purposes a large proportion of susceptible animals will develop the disease, as at this stage of the disease the infective spore-like cysts are present.

In 1905, I was able to confirm Schaudinn's work regarding the pathogenic nature of *Entamœba histolytica*. Half-grown kittens were used in my experiments, and 50 per cent. of those given rectal injections developed the disease, while 66 per cent. of the feeding experiments were successful. It will be noted that the latter method gave the best results, as eight of the twelve kittens experimented with developed dysentery, *Entamœba histolytica* being found in the feces and in sections of the diseased intestine. One of the animals developed an amœbic abscess of the liver, and this species of entamœba was found in the abscess contents as well as in sections of the abscess wall. The period of incubation varied from six to fourteen days, being slightly shorter in the feeding experiments than after rectal injection.

All the kittens experimented upon were carefully examined for amœbæ prior to the experiments, so as to rule out a previous infection. Both pure and mixed cultures of all bacteria that could be cultivated from the feces were fed and injected in order to control the tests, and in none of the kittens so treated did symptoms of diarrhea or dysentery develop, and at autopsy no lesions were found in the intestine.

In dysentery produced by the rectal injection of the infected material the lesions were usually localized in the rectum, and were not so severe, as a rule, as when the infection was acquired through the mouth. The lesions produced were typical of those occurring in amœbic dysentery in man, and varied in extent and severity with the length of time the infection lasted. The symptoms consisted of diarrhea, with the passage of blood-stained, mucous stools, containing multitudes of motile *Entamœba histolytica;* rapid emaciation with loss of appetite and strength; and

finally, death from exhaustion. In a few instances attacks of severe diarrhea were followed by a period of constipation, and the disease became chronic in nature. The longest period of incubation was fourteen days in a kitten injected per rectum, and the shortest period six days in an infection by the mouth.

The following protocols of autopsies will illustrate the lesions produced in kittens by *Entamœba histolytica:*

Kitten No. 1. This kitten was injected per rectum on October 19, and killed upon November 21, the first evidence of infection having appeared about October 30.

Autopsy: Body that of a half-grown kitten, greatly emaciated. The abdomen is greatly distended with gas. The mucous membrane of the anus appears swollen, and a considerable amount of blood-stained mucus is adherent to it. The subcutaneous fat has almost entirely disappeared, and the muscles appear dry and atrophied. The pleural cavities are free from fluid, and the lungs appear normal. The heart is greatly congested, and contains red clots in all the chambers. The liver is hypertrophied, deeply congested, and marked albuminoid degeneration is present, but there is no trace of abscess formation. The kidneys are congested, and upon section present the usual lesions of an acute parenchymatous nephritis. The omentum contains a small amount of fat, and is not inflamed. The bladder is filled with urine. The intestines are greatly dilated with gas and fluid. Upon external examination the large intestine appears swollen, is grayish in color, with small, darker colored areas scattered along it. Upon opening the large intestine the mucous membrane of the rectum is found considerably swollen and inflamed, but no ulcerations are present. Above the rectum for a distance of about 10 cm. the mucous membrane is much swollen and edematous, bright red in color, and between the folds a considerable amount of pus can be seen. For a distance of about 4 cm. from the upper end of the large intestine the mucous membrane is inflamed, being red, swollen, and edematous. In this area there are numerous ulcerations, covered in with bloody mucus; they are of small size, somewhat irregular in shape, and extend, in most instances, to the submucosa, although there are a few which extend to the muscular coat of the intestine; the edges are undermined, and many of the ulcers are covered with necrotic tissue, brownish yellow in color, which has to be removed in order to expose them. A few of the ulcers communicate beneath the mucous membrane. The small intestine shows a rather severe acute enteritis and the stomach an acute gastritis.

Kitten No. 3. This kitten was fed once with feces containing *Entamœba histolytica*, and seven days later developed diarrhea, the feces containing blood and mucus as well as numerous motile amœbæ. At the end of two weeks it died, having presented severe symptoms of amœbic dysentery during this time.

Autopsy: Body that of a half-grown kitten, greatly emaciated. Subcutaneous fat entirely absent, and muscles dry and much atrophied. The abdominal cavity is free from fluid, and the intestines appear normal externally. The pleural cavities are free from fluid, and the heart and lungs appear normal. The liver is brownish red in color externally, with irregular yellow motlings. There is a small abscess present at the dome of the right lobe, measuring 0.25 cm. in diameter, showing distinctly through the capsule of the organ. Upon section of the liver the cut surface appears greatly congested, the lobules are distinct, and no abscesses are found other than the one mentioned. The gall-bladder appears normal. The kidneys appear enlarged and congested, and upon section show an acute congestion, with some thickening of the cortex. Externally the large intestine appears slightly, if at all, congested, although the walls are markedly thickened. Upon opening the large intestine it is found filled with fecal material mixed with a large amount of pus and blood-stained mucus. About 1 cm. from the anus, which is blood-stained and covered with mucus, there is an area measuring 4 cm. in length, presenting the typical lesions of amœbic dysentery, as they are observed in man. The entire mucous membrane is swollen, congested, and edematous. Numerous nodular areas project into the lumen of the intestine, which, when incised, are found filled with a glairy material containing hundreds of *Entamœba histolytica*. There are also numerous ulcerations, more or less irregular in shape, with thickened and undermined edges; many are covered in with necrotic tissue which, upon being removed, show that the floor of the ulcer is formed by the muscular coat of the intestine. Many of these ulcers communicate with one another beneath the mucous membrane, and most of them have penetrated to the muscular coat. The remainder of the large intestine presents numerous ulcerations, typical of those seen in the intestine of patients who have died of amœbic dysentery. The lesions are most marked just below the ileocecal valve, where large areas of the mucous membrane have been destroyed, the muscular coat of the intestine being exposed.

Kitten No. 5. This kitten was fed with milk containing *Entamœba histolytica* several times before dysentery developed. The period of incubation was eight days from the date of the last feeding, but from that time until it was killed, three weeks afterward, the animal presented the symptoms of amœbic dysentery, there being gradual loss of appetite, emaciation, and a diarrheal discharge containing blood and mucus, with numerous motile *Entamœba histolytica*.

Autopsy: Body that of a half-grown kitten, much emaciated. Subcutaneous fat entirely absent and muscles much atrophied. The pleural cavities are free from fluid and the lungs and heart

appear normal save for congestion. Upon opening the abdominal cavity the small intestine appears congested externally. The liver is hypertrophied and greatly congested. The kidneys are congested and enlarged, and upon section show the lesions of an acute parenchymatous nephritis. The large intestine is dark gray in color externally, and is considerably thickened, especially toward the rectum. Upon opening the intestine it was found to contain much fecal material, mixed with blood, mucus, and pus. Commencing at the rectum and extending for about half the length of the large intestine the mucous membrane is greatly swollen, bright red in color, and contains numerous ulcers. The majority of the ulcers are spherical in shape, the edges are undermined and greatly thickened, and many are covered in with necrotic tissue. Upon removing this necrotic material the base of the ulcer is found to be formed by the muscular coat of the intestine. The ulcers present are typical of the amœbic ulcerations seen in the intestine of man in every respect. The remainder of the large intestine is black in color and gangrenous, the mucous membrane having been almost entirely destroyed, exposing the muscular coat throughout this portion of the intestine. About 4 cm. below the ileocecal valve there was a small perforation measuring about $\frac{1}{6}$ cm. in diameter.

The following interesting cases of experimental infection with *Entamœba histolytica* have been furnished me by Doctor Wellman. His data cover five kittens, of which four developed dysentery and one remained free from the disease:

Kitten No. 18. On August 20, 1910, 4 to 5 c.c. of feces containing the cysts of *Entamœba histolytica* were injected per rectum. The kitten remained apparently healthy until September 1, when entamœbæ were found in the feces. From this time on the animal grew steadily worse and the number of entamœbæ increased. The animal was killed September 21, and the following conditions were found at autopsy: Great emaciation; heart and lungs normal; liver enlarged, but with no abscesses. Kidney showed signs of nephritis. The mucous membrane of the large intestine was inflamed and edematous, and there were numerous small ulcerations, scrapings from which showed many entamœbæ. The small intestine and the stomach appeared to be somewhat injected. Doctor Wellman stated, "I should call the condition found a typical amœbic dysentery."

Kitten No. 19. The same technique was employed in infecting this kitten. The animal developed dysentery, and *Entamœba histolyticæ* were found in the feces. The autopsy record of this animal is not given.

Kitten No. 20. This kitten was fed with 4 to 5 c.c. of the same feces used in infecting the kittens already mentioned. After eight days entamœbæ were found in the stools, and the animal died on

the fifteenth day after infection. The following conditions were found at autopsy: The kitten was much emaciated; heart and lungs normal; liver swollen and congested, but showing no abscesses. The kidneys showed the evidences of nephritis. The mucous membrane of the entire large intestine showed typical amœbic ulcerations many of them burrowing in character. The scrapings from the ulcers showed numerous entamœbæ. The entire intestine appeared edematous.

Kitten No. 23. This animal was fed with the same feces, and entamœbæ appeared in the stools on the ninth day after feeding. It was killed on the eighteenth day after infection and the same condition found as in kitten 20, but the lesions were not quite so severe.

Kitten No. 24. This animal was fed with the same feces, but with negative results. No entamœbæ appeared in the feces, and no lesions were found in the intestine when the kitten was killed on the twenty-eighth day after feeding. This animal was considerably older than the others experimented with, and I have found that for successful results young kittens must be used, as full-grown cats are much more resistant to amœbic infection.

Wellman states in his letter that he considers the lesions produced experimentally in these kittens as identical with those of amœbic dysentery in man. More recently Werner, working at the Sailors' Hospital, in Hamburgh, has produced dysentery in cats with *Entamœba histolytica*.

He experimented with two strains of *Entamœba histolytica*, only one of which he found infective. He was able to produce dysentery in cats with this strain, but found that after six passages the organism lost its virulence. The incubation period varied from four to thirteen days, the average being nine days. Of six cats infected with this species four died, the duration of the disease varying from seven to twenty-four days, the average being fifteen days. The animals were infected per rectum. Werner states that the lesions were typical of amœbic dysentery, and were always confined to the colon, especially the lower portion. Guinea-pigs and rats were found to be resistant to infection with this parasite.

From the evidence which has been submitted I believe it is impossible to conclude otherwise than that *Entamœba histolytica* is the cause of a form of amœbic dysentery. The character of the lesions present in this condition, the constant association of this species with the lesions, and the production of similar lesions in susceptible animals with material containing *Entamœba histolytica* I consider conclusive proof that this parasite is a cause of amœbic dysentery in man.

Relation of Entamœbæ Tetragena to Disease. The experiments of Viereck, Hartmann, and Werner prove that this species produces a form of dysentery, although Hartmann believes that it is

not as pathogenic to cats as *Entamœba histolytica*. The incubation period in his experiments varied from eight to ten days, and the infection lasted from three weeks to one month. He states that at autopsy the cats presented the typical lesions of amœbic dysentery as observed in man, and that *Entamœba tetragena* was found in the tissues. Darling in a personal communication, states that cats infected with *tetragena* show a severe *enteritis*, especially in the ilium, and not a colitis, which I believe serves to distinguish the lesions of tetragena infections from histolytica, in which there is always ulceration of the colon; in his infections he evidently was not dealing with *Entamœba histolytica*.

Werner experimented with five strains of *Entamœba tetragena*, only three of which were found to be pathogenic. One of these was still infective after five, one after three, and one after one passage through cats, but they all lost their virulence after repeated passage. The incubation period in his animals varied from five to twelve days, and the disease lasted from three to twenty-five days, the average being seventeen days. He states that he did not find any marked differences between the lesions produced by *tetragena* and *histolytica*, and that he does not believe that the evidence supports the idea that one is less pathogenic than the other.

Werner describes an interesting experimental case in which a cat infected per rectum with a strain of *tetragena* developed dysentery after five days' incubation, the stools containing many entamœbæ. At the end of twelve days the animal died, and at autopsy typical amœbic ulcers were found in the lower portion of the colon, while the right lobe of the liver showed an abscess the size of a hazelnut upon the anterior surface. The pus from the abscess contained entamœbæ of the *tetragena* type.

Franchini reports the production of dysentery in a monkey by rectal injections of fecal material containing *Entamœba tetragena*. The monkey experimented upon had been under observation in the laboratory for over a year, was perfectly healthy, and repeated examinations of the feces before the experiment showed them to be free from entamœbæ. After the rectal injections of material containing *Entamœba tetragena* the animal developed an intense dysentery, the stools containing blood, mucus, and multitudes of entamœbæ identical in morphology with those injected. The animal died from the infection, and at autopsy ulcers were found in the large intestine, and *Entamœbæ tetragena* were demonstrated in sections of the diseased tissues.

In a personal communication, Dr. H. B. Fantham states that he was successful in producing dysentery in one of two kittens fed upon feces containing *Entamœba tetragena* from an infection contracted in Algeria. The kitten died in three weeks, and ulcertions were found in the intestine, which contained *Entamœba*

tetragena. His experiments in kittens with rectal injections of material containing this parasite were all negative.

I have had no personal experience with the experimental production of dysentery in animals with this species, but I consider the evidence sufficient to prove that it is capable of causing the disease in susceptible animals, and that it is a frequent cause of dysentery in man. I have found *Entamœba tetragena* in patients suffering from dysentery contracted in the Philippine Islands, Panama, and several of the United States.

Relation of Cultural Amœbæ to Disease. As several authorities have reported instances of the production of dysentery in animals with cultures of amœbæ, it is necessary to consider briefly this phase of our subject. I have already stated that it has been proved by numerous investigators that all cultural amœbæ that have been thoroughly studied belong to the genus *Amœba* and differ in morphology and life-cycle from the parasitic species belonging to the genus *Entamœba*, and that there is no sufficient proof that any of the latter species have been cultivated.

Prior to the work of Musgrave and Clegg several authorities claimed to have produced dysentery in cats with cultures of amœbæ, while others were unsuccessful in thus producing the disease. It is unnecessary to consider here the conflicting results obtained by such investigators as Kartulis, Vivaldi, Cassagrandi and Barbagallo, and Zaubitzer along this line, but the work of Musgrave and Clegg deserves special consideration. These authors were successful in cultivating numerous strains of amœbæ in symbiosis with bacteria from the feces of dysenteric patients and from liver abscess pus. They refused to accept the classification of Schaudinn, and considered that all amœbæ might, under certain circumstances, become pathogenic. They were successful in producing ulcerations of the intestine and liver abscess in monkeys with mixed cultures of their amœbæ and various bacteria, and in one instance they claim to have produced amœbic dysentery in man with a pure mixed culture of amœbæ isolated from the stools of a dysenteric patient.

In the light of present knowledge these experiments of Musgrave and Clegg have no value as showing the relation of entamœbæ to disease. The work of Hartmann, Werner, Whitmore, Walker, and the writer has proved conclusively that the amœbæ cultivated by these authors are not entamœbæ but free-living amœbæ, and the species with which Musgrave and Clegg claim to have produced dysentery in man is a typical free-living amœba of the *limax* type. The occurrence of dysentery after the administration of this culture can be explained in many ways: The culture may have become infected with the cysts of *tetragena* or *histolytica*, or the person may have become naturally infected or have been infected at the time of the experiment, for in a region such as Manila natural infections would be very difficult to guard against. As regards the lesions

produced in monkeys with cultures of amœbæ, it should be remembered that these animals suffer naturally from amœbic infection, and there is no evidence in the authors' papers that repeated examinations of the animals' stools were made for a sufficient period of time before the experiments to prove their freedom from entamœbæ.

The occurrence of dysentery in monkeys after feeding or injecting cultural amœbæ is probably explained, in the vast majority of instances, by the fact that at least two species of entamœba are parasitic in monkeys, as shown by Castellani and v. Prowazek, and that these species are capable of producing dysentery in these animals. Greig and Wells have also shown that in India natural amœbic infection in monkeys is very common; thus every one of fifty-three monkeys with which they desired to experiment showed amœbæ in the feces which resembled those found in man. These organisms only appeared at irregular intervals, so that repeated examinations of the feces were necessary in order to demonstrate them. Some of the animals presented symptoms of dysentery while under observation, while others appeared perfectly healthy. I do not know the percentage of monkeys infected with entamœbæ in the Philippines, but I personally observed three naturally acquired amœbic infections in these animals in Manila, and I have no doubt that careful examinations, covering a sufficient period of time, would demonstrate that a considerable percentage of monkeys in these islands harbor entamœbæ which could easily be confused with those parasitic in man.

In many of their (Musgrave and Cleggs) experiments the amœbæ were grown in symbiosis with the typhoid bacillus, and this mixed culture was injected directly into the liver, subcutaneous tissue, or the abdominal cavity of the animals used, and was followed by the appearance of abscesses containing both amœbæ and bacteria. It is well known that the typhoid bacillus is capable of producing abscesses when thus injected, and I have myself observed the formation of abscess of the liver after the injection of pure cultures of this organism into the organ, so that deductions based upon such experiments are valueless as proving the pathogenicity of any amœba. Even though lesions were produced in animals with these cultures of amœbæ, they would bear no relation to the disease as it occurs in man, because the cultivated amœbæ are entirely distinct from the true parasitic amœbæ which cause dysentery in man. Personally, I believe that some of the lesions described by Musgrave and Clegg were produced by the mixed cultures of amœbæ and bacteria with which they worked, but I cannot admit that the cultural amœbæ are identical with the parasitic species or that their experiments are of any value as showing the relation of the entamœbæ of man to disease.

The claim of Musgrave and Clegg that the differences in structure and life-cycle of the cultural amœbæ are due to artificial surround-

ings cannot be accepted. Walker in discussing this argument very justly says, "that while slight modifications might occur under such conditions, it is very improbable that cultivation could cause a complete reorganization of the structure of the nucleus, develop *de novo* such a constant organelle as a contractile vacuole, or profoundly modify the life-cycle of the organisms. Moreover, that the supposed modification should invariably take the form of a change from the characters of the genus *Entamœba* to those of the genus *Amœba* is, to say the least, improbable."

It is not difficult to explain the occurrence of free-living amœbæ in cultures made from feces, liver-abscess pus, or from the intestine at autopsy, if one remembers that the cysts of these species are present in the atmosphere, and may thus easily contaminate the cultural material. The recent observations of Liston and Wells prove that it is possible to secure cultures of free-living species of amœbæ upon media exposed to the air, the organisms in such cultures agreeing in morphology with those obtained in cultures from the feces and intestine. Though it is possible for the free-living species to pass through the intestinal canal of animals in an encysted state and afterward develop in cultures, it should be remembered that unless the most careful cultural techinque is used such amœbæ may contaminate the cultures from the atmosphere, and it is probable that this is the manner in which many cultures have been obtained, especially in regions where the free-living species are found abundantly. However, it is very difficult to understand how anyone possessing accurate knowledge of the morphology and life-history of amœbæ could mistake these cultural species for any of the entamœbæ of man.

The recent work of Williams, Wherry, and others showing that under abnormal stimulation by adding various substances to culture media, free-living or cultural amœbæ may assume appearances resembling the morphology of the entamœbæ, is of no value for in not a single instance has the nuclear structure of thecultural, forms been transformed into that of the entamœbæ of man.

Conclusions. The following conclusions appear to be justified as regards the relation of entamœbæ to disease.

1. *Entamœba coli* is a harmless commensal in the human intestine.

2. *Entamœba histolytica* and *Entamœba tetragena* are pathogenic species capable of producing in man the disease known as amœbic dysentery.

3. *Entamœba coli*, *Entamœba histolytica*, and *Entamœba tetragena* are strictly parasitic species and have not been cultivated.

4. There is not sufficient evidence at present to prove that any of the amœba that have been cultivated are pathogenic to man. All cultivated species belong to the genus *Amœba*, and differ greatly in morphology and life-cycle from the parasitic amœbæ, which belong to the genus *Entamœba*.

REFERENCES.

The references are arranged alphabetically, and only papers which have been consulted in preparing this paper are included in the list.

Ashburn, P. M., and Craig, C. F. Entamœba Coli, etc., The Military Surgeon, 1907, i, p. 21.

Casagrandi, O., and Barbagallo, P. Recersche Biolog. e. Cliniche dell "Amœba coli," Boll. Accad. Groinea. sc. nat. Catania, 1895, xli, p. 7.

Idem. Entamœba hominis a amoeba coli (Loesch), Anali d'Igiene sperimentale, 1897, v, p. 103.

Castellani, A. Note on a Liver Abscess of Amœbic Origin in a Monkey, Parasitology, 1908, i, p. 101.

Celli, A., and Fiocca, R. Ueber die Etiologie der Dysenterie, Centralbl. f. Bakt., etc., 1895, I, xvii, p. 309.

Craig, Chas. F. Observations upon Amœbæ Infecting the Intestine, etc., Amer. Med., Philadelphia, 1905, ix, pp. 854, 897, 937.

Idem. Studies upon Amœbæ in the Intestine of Man, Jour. Infect. Diseases, 1908, v, p. 324.

Idem. Entamœba Tetragena as a Cause of Dysentery in the Philippine Islands, Arch. Inter. Med., 1911, vii, p. 362.

Idem. The Parasitic Amœbæ of Man, Philadelphia, 1911.

Idem. Observations upon the Morphology of Parasitic and Cultural Amœbæ, Jour. Med. Research, 1912, xxvi, p. 1.

Idem. The Parasitic Amœbæ of Man and Their Relation to Disease, New Orleans Med. and Surg. Jour., 1912, xxx, p. 1.

Darling, S. T. Report of Department of Sanitation, Isthmian Canal Commission, March, 1912, p. 42.

Elmassian. Entamœba Minuta, etc., Centralbl. f. Bakt., etc., 1909, Abt. Orig., 52, p. 335.

Fantham, H. B. Personal Communication.

Greig, E. D., and Wells, R. T. Dysentery and Liver Abscess in Bombay, Scientific Mem. Sanitary Department, Government of India, 1911, N. S., 47.

Harris, H. F. Hatfield Prize Essay, Philadelphia, 1901.

Franchini, G. Experimentelle Tropendysenterie, die Entamoeba beim Affen, Centralbl. f. Bakt., etc., 1912, I Abt., Orig., 61, 7, p. 590.

Hartmann, M. Eine neue Dysentery Amoeba, Beiheft. z. Arch. f. Schiffs-u. Tropenhyg., 1908, v, p. 117.

Idem. Untersuchungen u. parasitischen amoeben., I, Entamoeba histolytica, Schaudinn, Arch. f. Protistenk., 1909, xviii, p. 207.

Idem. Die Dysenterie-Amoeben, Handbuch der Pathogenen Protozoen. v. Prowazek, Leipzig, 1911, I, p. 50.

Idem. Untersuchungen u. parasitische Amoeben, II, Entamoeba tetragena, Viereck. Arch. f. Protistenk., 1912, xxiv, p. 163.

Hlava. Ueber die Dysenterie, Centralbl. f. Bakt., etc., 1887, Abt. x, p. 537.

Huber. Deutsche. med. Wochenschr., 1903, xxix, p. 267.

James, W. M. Personal Communication.

Jurgens. Zur Kenntniss der Darmamoeben und der Amoeben-enteritis. Veroff. a. d. Geb. Milit-Sanitatswes, Berlin, 1902, xx, p. 110.

Kartulis. Zur Aetiologie der Dysenterie in Aegypten, Virchow's Arch. f. path. Anat., 1886, cx, p. 521.

Koidzumi, M. On a New Parasitic Amœba, Entamœba Nipponica, Centralbl. f. Bakt., etc., 1909, I, Orig., li, p. 650.

Kovacs, F. Amoeben Dysenterie, Zeitschr. f. Heilkunde, 1892, xiii, p. 509.

Kruse, W., and Pasquale, A. Studium des Dysenterie und Leberabscesse, Deutsche. med. Wochenschr., 1893, xv, I, p. 354; xvi, p. 368.

Lesage. Note sur l'Entamibe de la dysenterie amibiene, etc., Bull. d. l'Soc. d. Path. Exotique, 1908, I, p. 104.

Leidy, J. Fresh Water Rhizopods of North America, Government Printing Office, Washington, D. C., 1879.

Liston, W. G., and Martin, C. A. A Note on the Early Stages of Nuclear Division of the Large Amœba from Liver Abscesses, Quart. Jour. Microscop. Science, 1911, N. S., ccvi, p. 279.

Loesch, F. Massenk. Entw. v. Amoeben in Dickdarm, Virchow's Arch. f. Path. Anat., 1875, lxv, p. 196.

Musgrave, W. E., and Clegg, M. T. Amoebas: Their Cultivation and Etiological Significance, Bureau of Government Laboratory Bulletin, Biological Laboratory, 1904, 18, Manila, P. I.

Idem. The Cultivation and Pathogenesis of Amœbæ, Philippine Journal of Science, 1906, I, p. 909.

Noc, F. Sur la Dysenterie Amibiene en Cochinchine, Ann. Inst. Pasteur, 1909, xxiii, p. 177.
Prowazek, S., v. (and Hartmann, M.) Arch. f. Protistenk., 1909, xviii, p. 312.
Prowazek, S., v. Entamoeba Buccalis, N. S., Arb. a. d. kaiserl. Gesundheitsamte, 1904, xxi, p. 42.
Idem. Beiträg. zur Entamoeba-Frage (Entamoeba Williamsi), Arch. f. Protistenk., 1911, xx, p. 345.
Idem. Zur Kenntnis der Entamoeba, Arch. f. Schiffs-u. Tropenhyg., 1912, xvi, I, p. 30.
Idem. Weitere Beiträg zur Kenntnis d. Entamoeben, VI, Arch. f. Protistenk., 1912, xxvi, p. 241.
Schaudinn, F. Untersuch. u. d. Fortplanzung d. Rhizopoden. Arb. a. d. Kaiserl. Gesundheitsamte, 1903, xix, p. 547.
Sistrunk, W. E. Intestinal Parasites Found in Individuals Residing in the Northwest, Jour Amer. Med. Assoc., 1911, lvii, p. 1507.
Stiles, C. W. The Presence of Entamœba Histolytica and Entamœba Coli in North Carolina Public Health Reports, Washington, 1911, xxvi, p. 1276.
Strong, R. P., and Musgrave, W. E. Etiology of the Dysenteries of Manila, Annual Report of Surgeon General, United States Army, 1900, p. 251.
Vedder, E. An Examination of the Stools of One Hundred Healthy Individuals, etc., Jour. Amer. Med. Assoc., 1906, xxvi, p. 870.
Viereck, H. Studien über die in den Tropen erworbene Dysenterie, Arch. f. Schiffs-u. Tropenhyg., 1907, xi, Beiheft I, pp. 1–41.
Vivaldi. Le Amoebe della Dissenteria, La Riforma Med., Naples, 1894, x, p. 147.
Walker, E. L. The Parasitic Amœbæ of the Intestinal Tract of Man and Other Animals, Jour. Med. Research, 1908, xvii, p. 379.
Idem. A Comparative Study of the Amœbæ in the Manila Water Supply, etc., Philippine Journal of Science, 1911, Sec. B, vi, p. 259.
Wellman, Creighton. Personal Communication.
Wells, R. T. Aerial Contamination as a Fallacy in the Study of Amœbic Infections by Cultural Methods, Parasitology, 1911, iv, p. 204.
Werner, H. Studies Regarding Pathogenic Amœbæ, Indiana Med. Gaz., 1909, xliv, p. 241.
Whitmore, E. Parasitare and freilebende Amoeben aus Manila and Saigon, Arch. f. Protistenk, 1911, xxiii, p. 70.
Idem. Studien über Kultur amoeben aus Manila, Arch. f. Protistenk., 1911, xxiii, p. 81.
Williams, Anna. Pure Cultures of Amœbæ Parasitic in Animals, Jour. Med. Research, 1911, xxv, p. 263.
Zancoral. Pathogenie des absces du foie, Rev. Central. f. Bakt., etc., 1893, I, Abt., p. 638.
Zaubitzer. Studien über Strohinfus., amoebae, Arch. f. Hyg., 1901, xlii, p. 311.

BREAST TUMORS, WITH SPECIAL REFERENCE TO CARCINOMA.[1]

By A. Primrose, M.B., C.M. (Edin.), M.R.C.S. (Eng.),

Associate Professor of Clinical Surgery, University of Toronto; Surgeon to the Toronto General Hospital.

Tumors of the breast constitute a group of conditions presenting considerable variety and requiring great care on the part of the clinician in establishing an accurate diagnosis. The point of chief importance is to recognize malignancy when it exists and to make the diagnosis at the earliest possible moment in order that the patient may have the benefit of surgical intervention at a time when operation holds out the best prospect of cure.

[1] Read before the Canadian Medical Association at Edmonton, Alberta, August, 1912.

These tumors may be divided into two great groups—namely, the newgrowths, and those of inflammatory origin. Inflammation, both acute and chronic, is exceedingly common, giving rise to abscess formation or to mastitis without suppuration. Specific inflammatory conditions are those dependent upon the infective virus of tuberculosis, syphilis, or actinomycosis. Cystic tumors exist in the form of galactoceles, such as may originate in the lactiferous ducts or in the gland acini, or a cyst may form as a phase in the development of a newgrowth; an intracystic papilloma is not uncommon, and closely associated from the point of view of etiology is the cystic development found in the ordinary fibroadenoma. Dermoid cysts and hydatid cysts are sometimes found. The benign growth of most frequent occurrence is the adenoma or adenofibroma, presenting considerable variety in the development of the fibrous and epithelial elements respectively in individual tumors. Other simple growths are occasionally met with, such as angioma, myxoma, and lipoma. A mixed tumor resembling that found in the parotid gland has also been described. The malignant growths are usually cancer, but sarcoma develops in a small percentage of cases.

The breast is seldom the site of secondary growth, but metastatic tumors do occur in rare instances. Thus Plew recently reported a case of metastasis in the left mamma in a patient with pelvic sarcoma. He quotes 7 cases from the literature, 5 of these being carcinoma and the other 2 sarcoma. In my own clinic there was an example of secondary cancer in the breast, the primary growth being in the pelvis probably ovarian in origin. In this instance I had used the injection of ascitic fluid recommended by Hodenpyle a few years ago, and some of the injection had been made into the submammary tissue, so that there was some doubt as to whether it was a case of true metastasis or of implantation carcinoma.

While it is obvious that great variety is displayed in the development of newgrowths in the mammary gland, nevertheless the distinctive differences between the two great groups of benign and malignant tumors constitute by all odds the most important material for our study. Every effort should be made to define the cleavage where it exists between these two classes. The ultimate resources of laboratory investigation and clinical observation must often be combined in order to arrive at an accurate diagnosis. The clinical picture of advanced malignant disease is often too conclusive without further investigation being necessary, but frequently patients present themselves with a tumor of the breast where it is impossible to say from the clinical standpoint alone whether it is malignant or not, and again we must view with suspicion the pathologist who undertakes to exclude malignancy with absolute certainty by the examination of a "quick section" at the time of operation. Such an examination must necessarily be

incomplete when made while the operation is in progress. The positive report of the pathologist at such times is of the greatest possible importance but a negative report is of comparatively little value especially when taken apart from the clinical manifestations.

When we take into account all the methods at our disposal for arriving at a diagnosis we must come to the inevitable conclusion that today mistakes in diagnosis are much more common than are justifiable. I am sure that the experience of any general surgeon will coincide with mine in this regard and one who has the oversight of a surgical service in a large hospital must conclude, from the material that comes to his hand, that patients with breast tumor are not studied with sufficient care. The result is that incomplete operations are often undertaken or the terrible results of waiting for definite symptoms of malignancy become all too obvious before the surgeon is consulted. It is mainly because these facts have impressed themselves upon me very forcibly that I ventured to suggest a discussion on breast tumors before the Canadian Medical Association, with the hope that practitioners throughout the country might be awakened once more to their responsibility in this matter, and that further effort might be stimulated to increase our efficiency in the treatment of those unfortunates who are the victims of malignant disease of the breast.

The material which I have utilized for my observations include cases occurring in the various services of the Toronto General Hospital for eight years, from 1905 to 1912 inclusive, to which I have added cases from my private records. These cases may be summarized as follows:

MALIGNANT GROWTHS.

Toronto General Hospital cases:	Carcinoma	158		
	Sarcoma	3		
			161	
Private cases:	Carcinoma	54		
	Sarcoma	1		
			55	
Total				216

BENIGN GROWTHS.

Toronto General Hospital cases:	Fibroadenoma	58		
	Chronic mastitis	32		
			90	
Private cases:	Fibroadenoma	17		
			17	
Total				107
Grand total				323

A few observations of statistical value may be made from a study of these 323 cases.

Age. In malignant cases the oldest patient operated on was aged seventy-seven years, the youngest was aged twenty-eight years. The average age was 49.2 years.

Taken in decades the following table was constructed:

30 and under	3.4 per cent.
31 to 40 inclusive	17.5 per cent.
41 to 50 inclusive	40.0 per cent.
51 to 60 inclusive	19.0 per cent.
61 to 70 inclusive	14.0 per cent.
Over 70	5.6 per cent.

In benign cases the oldest patient operated on was aged sixty-one years, and the youngest was aged nineteen years. The average age was thirty-seven years.

Taken in decades the following table was constructed:

20 and under	3.0 per cent.
21 to 30 inclusive	23.0 per cent.
31 to 40 inclusive	38.5 per cent.
41 to 50 inclusive	27.7 per cent.
51 to 60 inclusive	6.0 per cent.
Over 60	1.5 per cent.

Sex. Of malignant cases there were 211 females and 5 males: Married females, 77 per cent.; single females, 21 per cent.; males, 2 per cent.

Where the record of childbearing had been made by the historian one found that there had been no children in 7 cases and one or more children in 54 cases.

Of benign cases there were 105 females and 2 males: Married females, 51 per cent.; single females, 49 per cent.

Of the 5 cases of malignant growth noted in the males 4 were carcinoma and 1 sarcoma. In 2 of these cases of cancer in the male there was a definite history of trauma. In 1 there had been a bruise followed by ulceration, and in 1 irritation of the nipple by braces, causing induration, followed by cancer development.

The history of this latter case in the male extended over thirteen years. He was aged fifty-two years, when he was operated upon for malignant tumor of the right breast; at the time of this operation trouble had existed for seven years. The breast and tumor were removed. Recurrence occurred locally and in the axillary glands, and he was operated on by the writer one year after the primary removal. He died of recurrence five years afterward.

In the case of the man suffering from sarcoma there had been a tumor in the breast for three years, which began to grow rapidly two months before operation. The axillary glands were not involved.

Clinical Manifestations of Malignancy. In making an excerpt of the histories of the 216 cases of malignant growth an effort was made to determine the relative frequency of certain manifestations of cancer of the breast by observing the number of times certain features were recorded by the historians. The following is the result in the order of frequency.

1. Tumor: Present in all cases.

2. Glandular involvement: Axillary glands involved and palpable in 36 per cent. Axillary glands noted as not involved in 6 per cent. Subclavicular glands involved and palpable in 1 per cent. Supraclavicular glands involved and palpable in 2 per cent.

3. Pain: Recorded in 24 per cent.

4. Skin involved: (That is, from mere puckering to marked involvement) 23 per cent.

5. Trauma given as a cause: 12 per cent.

6. Ulceration: In 9 per cent.

7. Retracted nipple: Noted in 6 per cent.

8. Discharge from the nipple: Noted in 5 per cent. In half of these cases the discharge was bloody and in the remainder the character was not stated.

9. Sore nipples in the previous history: This was usually described as "cracked nipple," and was recorded in 3 per cent.

It is noteworthy that the most obvious features in the clinical history of patients presenting themselves with malignant trouble of this kind consisted of a tumor in the breast, with palpable glands in the axilla. Pain was frequently complained of, and there was often more or less involvement of the skin. These were the signs of malignancy which were emphasized as the most significant manifestations of malignancy by our predecessors a quarter of a century ago. By them too retraction of the nipple (which was noted in 6 per cent. of my cases) was considered a most important sign. We should not wait for such signs. It is true that in a given case these conditions will manifest themselves sooner or later, but by that time all chance of saving the patient's life in the vast majority of cases will have disappeared. Unfortunately there are practitioners still who wait for the more certain signs of malignancy before sending their patients to the surgeon. I trust that all will join with me in urging that the qualified practitioner of today who advises his patient to wait for the grosser signs of malignancy is most seriously—I had almost said criminally—negligent.

Let us now inquire into the methods at our disposal in making a diagnosis. At the outset we must admit that a definite diagnosis is often impossible. There are, on the one hand, certain cases of malignant growth which simulate the benign and it is equally true that a benign growth may present features suggesting malignancy. A case, however, which seems doubtful when we first see

it may often be diagnosticated correctly when we use all the means at our disposal to establish the diagnosis.

The age of the patient should make us suspicious. We have seen that the largest proportion of patients with malignant disease are aged between forty and fifty years; nevertheless, we have patients under thirty years as well as very aged women with breast cancer. The character of the tumor itself and its immediate connections must be carefully examined. The cancer growth, usually single and very firm, moves with the breast tissue and not independently of it. At an early period the skin over the tumor is not as freely movable as it is over the normal breast tissue. This test should be tried in a very delicate fashion, placing the fingers on either side of the growth and sliding the skin over it in various directions. The development of the tumor causes a pull upon the ligaments of Cooper, and this puckers or dimples the skin more or less definitely when one attempts to slide it from side to side. The atrophy of the subcutaneous fat immediately over the tumor has also been described as a cause of this puckering. This test can be elicited long before any demonstrable infiltration of the skin and subcutaneous tissues by the growth has occurred. It is not necessary to refer in particular to invasion of the skin, with or without ulceration, phenomena which are characteristic of advanced cancer. Retraction of the nipple too is in evidence as a rule in late cases only. When it is present it is a very strong argument in favor of malignancy. Bloody discharge from the nipple has been looked upon by some as pathognomonic of cancer, but in rare instances a duct papilloma may give rise to it. In a recent paper published by Mintz, of Moscow, the author reports 7 cases of bloody discharge from the nipple and had previously reported 8 cases of serous discharge which he calls "catarrh of the mamma." From his microscopic examinations after amputation he is led to conclude that both forms of discharge indicate proliferative changes in the gland resulting in adenomatous growth or actual carcinoma. Hence, he advocates radical treatment in all these cases. Both forms of discharge, he points out, develop about the climacteric, when involution of the mamma begins.

Both breasts should be examined. The existence of a tumor in each breast is in favor of a diagnosis of a simple growth, but one must assuredly note that there may be a cancer in each breast. Thus in my series there were 4 cases of bilateral development of carcinoma.

The lymph nodes in the axilla are invaded at an early date. No matter how early we operate it is rare for the pathologist to fail to find cancer in the axillary lymph glands. These glands too are, one believes, much more frequently palpable than our clinical records would lead us to suppose. The axilla should, therefore, be explored most carefully by the examining finger in order to

determine whether or not these glands can be felt. Halsted reports 2 cases where cancerous axillary glands due to malignant disease in the mamma, had attained conspicuous dimensions before the breast tumor appeared.

The history as to the duration of the tumor is of little or no value in helping us to a diagnosis. Thus of those cases that came to operation in my series one finds a history extending over varying periods. The shortest was one week and the longest twelve years. The history as to this point in benign cases is very similar.

Turning now to the constitutional effects of malignancy, apart from the local trouble. Emaciation and the cancerous cachexia are symptoms the significance of which is all too obvious in late cancer. It is well, however, to inquire as to loss of weight because even in doubtful cases we occasionally have our suspicions confirmed by a definite positive history in this regard. On the other hand, cancer sometimes exists for a long period without any obvious failure of nutrition. An attempt has been made in recent years to determine whether or not examination of the blood would yield some information of diagnostic value. We do not refer to the kind of blood analysis for which so much was claimed by the plaintiff in a recent famous lawsuit in England, regarding which, in spite of the finding of the Court, I think we may safely assume the test to be of no scientific value. The study of hemolysis for diagnostic purposes has attracted some attention. Thus Weil and Crile have used human serum and human corpuscles for the purpose. In Crile's cases hemolysis was not obtained in 125 normal cases but was observed in 82 per cent. of cases of carcinoma. Whittemore at a more recent date obtained hemolysis in 7 out of 109 normal cases (17 per cent.), while in 22 cases of carcinoma it occurred in 8 cases only (36 per cent.). Hemolysis also occurred in 50 per cent. of tuberculous cases and was found also in Hodgkin's disease, chronic empyema, etc. These results would lead one to believe that the test is of little diagnostic value. Weil showed that while the serum of cancer patients was destructive to normal red cells, the red cells of cancer patients are more or less resistant. Crile states that while the test must not be considered as a specific, yet he believes it to be of diagnostic value particularly in early cases, in all of whom, he thinks a hemolytic serum exists. A complement-fixation test, similar in principle to the Wassermann reaction, has been employed, using the antigen of carcinoma cells. The test is useless in diagnosticating syphilis from cancer as the sera of the former are sometimes positive to this test. Lastly, it has been found that normal sera have the power of breaking up cancer cells *in vitro*. It is, therefore, obvious that the study of the blood yields results which may have a very significant bearing on the question of establishing a diagnosis of cancer. In the meantime, however, we cannot say that the specific value of the blood test has been definitely determined.

In doubtful cases at the time of operation one may employ the method introduced by Stiles, of Edinburgh, known as the "nitric acid test." It is as follows: "Place a sliced lump in 5 per cent. solution of nitric acid for a few minutes and then wash in running water; the epithelial elements will be rendered opaque by the coagulation of the protoplasmic epithelial cells, while the connective-tissue elements are rendered more or less translucent or gelatinous. By observing the amount, arrangement, and distribution of the epithelial elements one can almost invariably say if it is cancer or a mastitis or hypertrophy of the ultimate globules of the gland parenchyma."

Again we may obtain a report from the pathologist at the time of operation by removing a portion of the growth for the purpose. This is the so-called "quick section." The surgeon waits for the report from the pathologist and completes the operation according to the findings. Or, again, the breast and tumor may be removed and the wound closed; the pathologist then makes a careful and complete examination of the tissues, and if malignancy is found the radical operation is completed a few days later. These operations for diagnostic purposes should, however, be avoided if possible. Most surgeons agree that there is considerable risk of disseminating the disease by manipulations of this kind. At all times in operating for malignancy we should handle the breast very gently and disturb the diseased tissues as little as possible while we make our incisions wide of the trouble through healthy tissue. A deliberate incision through the focus of cancer is by no means devoid of danger. It is far less reprehensible to do the radical operation with a mistaken diagnosis of malignancy than it is to spread the disease more widely in our effort to secure an absolutely accurate diagnosis. Again we should be on our guard when we receive a negative report from the pathologist who examines a quick section. We cannot agree with Rodman who states that he always relies upon frozen sections in hospital practice. Such a report is by no means conclusive, when positive findings of cancer are not made. Let me illustrate by reference to a case in my own practice:

Mrs. A. A., aged forty-nine years, had a lump under the nipple of the left breast for three years. Increased rapidity of growth occurred shortly before she consulted me. There was no retraction of the nipple but an axillary gland was palpable. I proceeded at once and did the radical operation. It happened that the axillary gland was lost for a time in the laboratory and the pathologist (a most competent and experienced worker) reported that the breast tumor was not malignant. Subsequently the axillary gland was found and on section proved to be malignant. A careful and prolonged search was now made of the breast tumor and eventually an undoubted focus of malignancy was found, which had hitherto escaped observation.

Such a case illustrates the futility of trusting to a negative report in a frozen section. It further emphasizes the importance of making a most careful search through all growths which appear benign in the first series of sections. Different parts of the tumor should be searched for evidence of malignancy before a final verdict is given. The conditions here may be compared to those found in the prostate gland where we believe malignancy is much more common than we had hitherto imagined. Careful search of the so-called "enlarged prostate" not infrequently demonstrates the existence of a focus of cancer which had not been suspected and somewhat similar findings are recorded in tumors of the mammary gland.

Another suggestive case occurred in my series, in which a patient, aged forty-nine years, had a growth removed from the breast which was reported as an adenoma by the pathologist. She returned seven months afterward with what proved to be a recurrent carcinoma at the site of the former operation.

Bloodgood is reported as saying at a recent meeting of the American Medical Association: "In my experience after one has had a sufficient training, the diagnosis from the gross appearance is easier, quicker, and in many cases more certain, than from a rapid frozen section."

If, therefore, with the most skilled assistance in establishing a diagnosis, and after using all the means available to that end, we are occasionally misled, we are inevitably driven to the conclusion expressed in the surgical axiom: "Any lump in any woman's breast is better out than in" (Finney). Greenough and Simmons come to a similar conclusion in the study of fibroepithelial tumors of the mammary gland.

The fact that malignant degeneration of benign growths in the breast is of frequent occurrence is obviously another convincing argument for the removal of all breast tumors. A recent study by Speese showed that no less than 26 per cent. of the cases of chronic cystic mastitis (that is, that form of "abnormal involution" occurring at the menopause) examined by him showed malignancy. So too cyst adenomas are found associated with carcinoma, the frequency of such association being placed by some authors as high as 15 per cent. Inflammatory conditions of the breast resulting in mastitis are often found in the early history of cancer cases. All these facts point conclusively to the frequent occurrence of malignant degeneration in benign growths of the breast.

Operative Treatment. The so-called "radical operation" should be carried out in all cases of malignancy. The skin incisions should vary in direction with the individual case, and should be so planned that a wide area is removed leaving an ample margin round about the site of trouble. The whole breast and both pectoral muscles (except perhaps the clavicular portion of the pectoralis major),

with the fat, fascia, lymph vessels, and glands of the axilla, are removed *en masse*. It is not necessary to dwell in detail upon the steps of such an operation because the technique is fully described in all modern text-books and the necessity for such radical procedure is practically universally admitted.

One is forced to believe that the part of the radical operation which is not done with the degree of thoroughness, which is so essential, is the removal of the gland-bearing fascia and fat along with all lymphatic tissue having connections with the mammary gland. The principal lymphatic channels of the mamma pass to the axillary group of glands. While this is fortunately the case one must remember that other channels exist through which the disease may be disseminated. Oelsner and Poirier have demonstrated undoubted connection between the internal mammary group within the thorax and the breast by means of a small lymph channel traversing the great pectoral muscle and passing through the fourth interspace at the level of the costochondral articulation. Fortunately these glands are not frequently involved, a circumstance which may be accounted for by the atrophy of this channel in senile mammæ, in which cancer usually develops (Poirier). The subclavicular glands are more likely to be involved. Rotter and Stiles have demonstrated the actual spread of cancer through the great pectoral muscle along afferent vessels, which, having perforated that muscle, run between it and the pectoralis minor and reach the subclavicular group of glands. These lymph channels accompany the thoracic branch of the acromiothoracic artery. The writer has recently demonstrated the implication of these glands in 2 cases when operating before his clinical classes. Grossman has succeeded in injecting these lymphatics in the dead subject. Implication of this group is much more likely to occur where the pectoral muscle is invaded by the cancer growth. Obviously, therefore, we have here a strong argument in favor of the routine removal of both pectoral muscles and of a thorough clearance of the uppermost part of the axillary space. The axillary vein and often the lower part of the subclavian must be cleaned thoroughly in the dissection. In rare instances the vein has been sacrificed. Thus, Stiles has removed portions of the axillary and Strunikow has recently reported 2 cases in which he resected the subclavian vein. In these cases there was only temporary edema of the arm.

The work of Sampson Handley has called special attention to the route of visceral invasion in breast cancer and he has given convincing demonstration of the spread from the primary focus along the lymphatic plexus of the deep fascia to the epigastric angle, where through the parietes immediately below the ensiform cartilage invasion of the abdominal cavity occurs. Thus we are forced to believe secondary deposit in the liver occurs and by this

route, too, Handley thinks we may have secondary invasion of the pelvic viscera (for example, ovary or uterus), once the peritoneal cavity has been reached, the action of gravity accounting for the fact that secondary tumors are found most abundantly at the lower limits of the serous cavity. These observations of Handley have induced the writer to follow his practice and to extend the field of operation so as to remove the fat and fascia over the epigastric triangle with the object of safeguarding the possible visceral invasion from that area.

Results. The best statistics available indicate that we are dealing here with a most treacherous and deadly disease. Stiles in the discussion before the British Medical Association, in 1908, stated that from 40 to 50 per cent. were permanently cured if a thorough operation were done. Cheyne, some eight years ago, claimed 57 per cent. of cures, his figures being based on the supposition that a cure was assured when a period of three years had elapsed after operation without recurrence. The three-year limit had been suggested by Volkmann. Jonas, in 1907, showed that 56.7 per cent. of his cases were free from recurrence after three years. Barker, on the other hand, claimed that 30 per cent. of those living three years after operation died of cancer. The fallacy of basing a claim for permanent cure after the lapse of three years is obvious to all. Many of us could report recurrence after an interval of eight, nine, or ten years of apparent immunity. Steinthal, of Stuttgart, has recently published a paper in which he gives statistics of three series of cases. The first series had been reported in 1905 and again in 1908, the second series in 1908, and all three series were tabulated in a paper written this year. The first series, therefore, was published at three-year intervals on three successive occasions. The percentage of cures claimed in the milder cases of the first series was 78.5 per cent., but this dropped in 1908 to 71.4 per cent., and in 1911 to 64.2 per cent. In the more severe cases the percentage of cures claimed in 1905 was 29.4 per cent., in 1908 it was 26.4 per cent., and in 1911 it had fallen to 23.5 per cent. Similar facts are elicited in the other series to show that if these cases are followed up and late recurrences recorded we shall find that our statistical tables based on short-time limits are of little value. Steinthal has expressed the opinion that between 25 to 30 per cent. of all cases are permanently cured by operation.

Korteweg at the Surgical Congress at Brussels enunciated a somewhat paradoxical thesis that the prognosis in cancer was the more favorable the later it was operated upon. By which he apparently meant that if a cancer had existed for a prolonged period without apparent increase or spread, then a radical operation would hold out a better prospect of permanent cure than would be the case were the operation done early. The statistics of Steinthal do not, however, support this theory, and I fancy

it is one which will not appeal to us as a safe guide for our treatment of these cases. It is apparently true that there is an attempt at natural cure in carcinoma. Sampson Handley believes this is brought about by a perilymphatic fibrosis.

We are familiar with the complete fibrosis which occurs in those rare cases of so-called "atrophic scirrhus," in which the patient lives on and may finally die of some intercurrent disease. I might refer to a patient who came under my observation who died at the age of eighty-three and who was known to have had cancer of the breast for twenty years, but which showed no sign of active growth until a few months before she died.

Spontaneous disappearance of cancer has occurred in rare instances. Hitherto effort made to discover some agent which would promote the natural arrest of cancer has proved unavailing. The effect of the *x*-rays is disappointing—superficial nodules disappear, but are almost certain to recur. It has been suggested by some that excessive use of the *x*-rays may be prejudicial, because it is known to destroy leukocytes, and may thus interfere with the inflammatory reaction, which is apparently such an important factor in bringing about a permanent cure. We know little of the permanent effect produced on the tissues by either the *x*-rays or radium in malignant disease.

Recently, I operated on 2 cases at the instance of Dr. W. H. B. Aikins, who has given a postoperative course of radium treatment: One was a case of carcinoma of the breast in a woman, aged forty-three years, with a tumor of a year's duration, involving the whole breast. It was adherent to the pectoral muscle, and the skin was involved with a mass in the axilla. Operation appeared to hold out little hope of success, but we deemed it worth while to try the combined effect of an extensive radical operation and subsequent course of radium. The other case in which radium was tried was in a woman, aged thirty-seven years, suffering from a sarcoma of the breast. Twenty months prior to my operation she struck the left breast and a tumor developed at the seat of the injury. A short time afterward she became pregnant and a child was born. She used the affected breast to some extent in nursing the child, but the lump became painful, and was incised when pus was said to have been evacuated. Ten days subsequently the lump was removed, and on recurrence after a short interval was again removed. At the time of my operation she had a recurrence in the scar, which was adherent to the pectoral muscles below. There were no glands palpable in the axilla. A radical operation was performed, and Dr. Aikins gave her a postoperative course of radium treatment. It is now four months since the operation, and there is no further sign of local trouble, although a series of rapid recurrences had occurred previously.

It is too early to speak of the result of treatment in these two instances, but when we have a "borderland" case it seems wise to give the patient the benefit of whatever line of action holds out the slightest prospect of relief.

Let me here enter a strong protest against submitting patients to operation where the condition is obviously too far advanced for relief by surgical measures. For example, patients with visceral involvement or with bone matastases are obviously beyond hope of relief. Invasion of the bony framework of the chest wall, or a mass of glands lying above the clavicle are equally hopeless and should not be subjected to operation. These are cases in which we believe the doctrine of Hippocrates holds true when he says that cases of cancer will live a long time if not interfered with by surgical means. In other words, we know that operation in these cases simply hastens the final issue. Let me give you an example of such a case. The history is as follows:

Mrs. X., aged forty-eight years. Ten months prior to consultation she had a bloody discharge from the nipple. A tumor had existed for four months. She now had a tumor implicating the whole breast, with ulceration about the nipple. It was markedly adherent to the deeper structures, with a mass of involved glands in the axillary and subclavicular region. The case was pronounced inoperable, and the patient so advised. She subsequently went to one of the best-known general hospitals in the United States, where a prominent surgeon removed the breast by radical measures, but after resecting part of a rib and finding the pleura involved, he desisted and closed the wound. The patient died in the hospital a few days afterward.

Such cases are better left alone not only for the patient's sake but because such measures strongly impress the laity, and women hesitate to submit to surgical procedures which prove so disastrous.

Some surgeons (for example, Gosset) remove the involved supraclavicular glands after temporary resection of the clavicle, but the hope of radical relief by such measures is so remote that one may discard such a proposition. The practice in the Mayo clinic is more commendable, where if the supraclavicular glands are enlarged it is their custom to excise one under local anesthesia, and if it proves to be malignant, no operation is advised, since it is probable that other and inaccessible regions are involved. (Judd.)

The functional result after the radical operation is remarkably good. It is important, if possible, to save the subscapular nerves and the posterior thoracic, otherwise an important group of muscles will be paralyzed, leading to very marked disability.

The mortality after the radical operation is wonderfully low considering the extent of the procedure. We realize this when we find the late Dr. Maurice Richardson, of Boston, reporting 1500 breast operations, with a total mortality of 4. In the series pub-

lished herewith there was a mortality of 3.2 per cent. after operation for malignant disease of the breast. As these included recurrent cases such as appear in a general hospital clinic, the mortality is not high. In my own private cases there was no operative mortality.

Recurrences. Of the 216 cases of operation for carcinoma of the breast we find that in no less than 42 (19.4 per cent.) were operations undertaken for recurrence. Of these, however, only 8.3 per cent. were recurrent after a radical operation. The following is the summary:

TABLE OF THE RECURRENT CASES WHICH ARE INCLUDED IN THE SERIES OF 216 PATIENTS.

Recurrence after radical operation	18 cases	8.3 per cent.
Recurrences after incomplete operation:		
Breast and axillary glands	1 case	
Breast and tumor	2 cases	
Tumor only	17 cases	
Total	20 cases	9.3 per cent.
Recurrences but no facts in history	4 cases	1.8 per cent.
Total cases	42 cases	19.4 per cent.

The youngest patient operated on for recurrence was aged twenty-nine years. The oldest patient operated on for recurrence was aged seventy-seven years. The average age of patients operated on for recurrence was forty-eight years.

The longest period elapsing before operation for recurrence: After radical operation, three years; after incomplete operation eight years.

The shortest period elapsing before operation for recurrence: After radical operation, three months; after incomplete operation, three months.

The average period elapsing after radical operation before the operation for recurrence was performed was 14.2 months.

The average period elapsing after incomplete operation before the operation for recurrence was performed was 23.4 months.

It would obviously not be fair to take this table as indicating the proportionate number of recurrences after the radical operation and after the incomplete operation respectively unless we remember that during the period under review (1905 to 1912) the number of incomplete operations yielding results would be few, because there must necessarily be few surgeons who would do other than a radical operation in cancer of the breast unless indeed there were a mistaken diagnosis. In spite of these facts, however, we find the recurrences after radical operation presenting themselves were fewer than after the incomplete operation. From these figures we may in fact assume that recurrence is a much rarer event after the radical operation than after the incomplete operation.

Another fact which comes out in these statistics is that no fewer than 17 cases came to operation for recurrence where the tumor only had been removed. On going into the history of these 17 cases one is justified in concluding they were cases of cancer when first operated upon. If this be the case then it is indeed time we should protest against the practice, which one fears is much too common, of removing a breast tumor without establishing a definite diagnosis in every instance. If a pathological laboratory is not available in the remote parts of the country where these operations are of necessity occasionally undertaken, then it is a simple matter to send the specimen to some larger centre for pathological report, and then the case may be dealt with according to the findings without undue loss of time.

It will be noted that the longest period elapsing after the radical operation before the operation for recurrence was three years and after incomplete operation eight years. The average period elapsing was after radical operation 14.2 months, and after incomplete operation 23.4 months. The numbers under review are perhaps not sufficiently large for definite conclusions, but they suggest that where recurrence does take place it is more rapid after the radical operation than after the incomplete one. The writer is unaware of any observations on this point. It is obviously one well worth noting, and should be further investigated.

Murphy believes the final results in carcinoma of the breast have not been materially improved in the last quarter of a century. He states that cases that have no demonstrable lymphatic metastases at the time of operation remain well in a considerable percentage of cases exactly as they did with our forefathers who excised breast tumors and did nothing else. He believes, however, that any hope of improvement in our results lies in early recognition and prompt removal of the disease.

In reviewing my series of cases one endeavored to determine the length of time the tumor had existed prior to surgical relief. The following table was constructed:

AVERAGE DURATION OF DISEASE AT TIME OF OPERATION.

Malignant growths: Average duration	14.375 months
(This does not include 2 exceptional cases where the duration was said to have been twelve years. Exclusive of these 2 the longest period was eight years and the shortest one week.)	
Those who came to operation under one year	54.5 per cent.
Those who came to operation under six months	35.4 per cent.
Those who came to operation under three months	19.0 per cent.
Those who came to operation one month and under one month from initial symptoms	8.4 per cent.
Benign growths: Average duration, adenofibroma	15.8 months
(This does not include one exceptional case of fifteen years and another of twenty-four years.)	
Chronic mastitis	2.9 months
(This does not include an exceptional case of thirteen years.)	

It appears to the writer that the foregoing table is significant, showing as it does that nearly 50 per cent. of our patients are allowed to go untreated for a whole year before they come to operation. On the other hand, only 8 per cent. come to us during the first month of trouble. Can anyone doubt that our percentages of cure would be vastly increased were the figures reversed? It is to be hoped that the time is not far distant when women will of their own initiative seek the advice of a practitioner of medicine whenever a tumor of the breast appears and that the doctor in turn will insist upon an immediate diagnosis being made. In the event of cancer being found then the modern radical operation will be carried out with the best possible prospect of saving the life of the patient. The writer is optimistic enough to believe that sooner or later such a desirable state of affairs will be brought about, and then the surgeon will be able to show vastly improved results in the operative treatment of this terrible malady.

LITERATURE.

Crile, G. W. On Cancer, Illinois Med. Jour., July, 1910.

Finney, J. M. T. "Surgery of the Breast," Surgery, its Principles and Practice, edited by W. W. Keen, 1908, iii, 563.

Gosset, A. Ablation du Cancer du Sein, Jour. de Chir., 1908, p. 321.

Greenough, R. B., Simmons, C. C. Fibroepithelial Tumors of the Mammary Gland, Annals of Surgery, October, 1911, p. 517.

Halsted, W. S. The Results of Radical Operation for the Cure of Cancer of the Breast, Trans. Amer. Surg. Assoc., 1907, xxv, 61.

Handley, W. Sampson. Cancer of the Breast and its Operative Treatment, London, John Murray, 1906.

Judd, E. S. Observations on the Present Status of Surgery for Cancer of the Breast, New York Med. Jour., April, 1912, p. 867.

Mintz, W. Zur Pathologie und prognostischen Berwertung des Serosen Katarrhs der Brustdrüse und der bludenden Mamma, Zent. f. Chir., 1912, Nr. 10, p. 313.

Murphy, J. B. Carcinoma of the Breast, Surgical Clinics of John B. Murphy, February, 1912. p. 12.

Plew, H. Ein Fall von Beckensarkom mit Metastase in der linken Mamma, Berliner klin. Woch., 1912, Nr. 18, p. 832.

Richardson, Maurice H. The Operative Treatment of Cancer of the Breast, Jour. Amer. Med. Assoc., 1911, lvi, 315.

Rodman, W. L. The Diagnosis and Treatment of Benign Tumors of the Breast, Trans. Amer. Surg. Assoc., 1910, xxviii, 456.

Speese, John. Malignant Degeneration of Benign Diseases of the Breast, Ann. Surg., 1910, li, 212.

Steinthal, C. Weitere Mitteilungen über operative Dauerheilungen beim Mammacarcinom, Beiträge zur Klinischen Chirurgie, 1912, Band lxxviii, p. 669.

Stiles, H. J. Discussion on Cancer of the Breast, British Med. Jour., October, 1908, p. 970.

Strunikow, A. Zur Resection der Vena Subclavia, Zent. f. Chir., 1911, Nr. 16, p. 590.

Symposium of Breast Cancer, Various Papers, Trans. Amer. Surg. Assoc., 1907, xxv, 62 to 212.

Poirier, P., and Cuneo, B. The Lymphatics, English edition, translated and edited by C. H. Leaf. Chicago: W. T. Keener & Co., 1904.

Whittemore, Wyman. The Value of Hemolysis in the Diagnosis of Cancer, Publications of the Massachusetts General Hospital, 1909, No. 2, ii, 755.

THE RELIEF OF GASTRIC CRISES IN TABES DORSALIS BY RHIZOTOMY.[1]

By Charles H. Frazier, M.D.,

PROFESSOR OF CLINICAL SURGERY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Though surgery of the spinal nerves is still of comparatively recent origin, nevertheless such remarkable advances have been made in this field during the last few years, and so much suffering and almost intractable pain have been alleviated, that we can scarcely feel too sanguine as to its future. Since Abbé and Bennett, in 1888, first conceived the idea of resecting the posterior spinal roots for the relief of neuralgia of the brachial plexus, similar operations have been performed by Horsley, Chipault, Duplay, and others for the relief of intractable pain. For example, rhizotomy was performed by Faure in a case of inoperable tumor of the uterus and by Giordano for the relief of sciatica. In 1900 Mingazini[2] proposed intradural resection of posterior sacrolumbar roots in a case of tabes, with severe lightning pains in the legs, but rhizotomy was not performed.

Gastric crises of tabes were described as early as 1851 (Romberg and Grube), but they have been well known only since Charcot's classic description of them in 1868. The excellent researches of Head and others have proved quite conclusively that disorders of this nature are of nervous origin. The crises are oftentimes one of the earliest stages of the disease, and increase in severity until the patient's life is menaced by the excessive denutrition and the morphine habit, to which he almost inevitably is forced to resort, and while life itself lasts, the suffering is so terrible that he is ready to try almost anything which promises relief. Numerous therapeutic measures have been used, such as lumbar puncture, epidural injections of stovain and novocain, the alternating current, and the *x*-ray treatment, but these have brought sometimes only transient relief and sometimes none at all.

One of the earliest operations for the relief of this condition was carried out by Vallas and Cotte[3] in 1906, on a patient who for six years had suffered from lancinating pains and uncontrollable vomiting. The abdomen was opened and the stomach found to be normal; the solar plexus was then freed from the celiac axis and stretched. The crises ceased immediately and did not appear again during the time which elapsed before the case was reported to the Society of Medicine of Lyons, on March 26, 1906. There is no record of this procedure being imitated.

[1] Read before the Philadelphia Neurological Society, April 26, 1912.

[2] Neurolog. Centralblatt, 1910, No. 8.

[3] Révue neurologique, 1907, p. 27.

In 1908 Förster aroused the interest of surgeons by conceiving the idea of resecting certain posterior dorsal roots in severe cases of crises in which all other forms of treatment had failed. This procedure is justified on the theory that the crises are due to irritation of the sensory sympathetic fibers of the stomach, which, after entering the celiac plexus in the splanchnic major nerve, pass to the spinal cord through certain posterior dorsal roots. This irritation manifests itself in the severe pain and vomiting, in the tremendously increased hyperesthesia of the skin of the epi-, meso-, and hypogastrium, and in the exaggeration of the epigastric reflex. If we concede this hypothesis, and if we agree with Head that the sensory fibers innervating the stomach are the seventh to ninth posterior dorsal roots, then we cannot but acquiesce in Förster's suggestion of resecting these nerves, thus intercepting the sensory pathway to the stomach, to relieve the crises.

On the other hand, it has been proved that the stomach is supplied by sensory fibers from the pneumogastric nerve, representing the central nervous system, as well as by the sympathetic. Eppinger and Hess[4] came to the conclusion through their physiological experiments that visceral crises are to be explained by irritation and later paralysis of the autonomous nervous system (vagus nerve), thus laying stress on the motor rather than on the sensory irritation. On these grounds Knapp and many surgeons are skeptical as to the value of Förster's operation for the relief of visceral crises, as they think the nerve supply of the stomach is much more dependent on the vagus than upon the sympathetic.

Indeed, during the last year Exner[5] proposed the resection of both vagus nerves for the relief of gastric crises in tabes, and in order to avoid any untoward complications, he advises that this operation be followed by a gastrostomy and the introduction of a drain from the stomach to the duodenum. After about three weeks the drain may be removed. Exner considers this procedure much simpler than rhizotomy and feels that its results will be even more satisfactory. In his first case, the vomiting and pains in the epigastric region ceased, while the lancinating pains in the legs and the hypogastrium remained. This was the condition three months after the operation. In his second case, the vomiting stopped after the operation, but the pain in the epigastrium was very severe and atony of the stomach was pronounced up to the time of the patient's death three weeks after the operation. Owing to the satisfactory results of his first case, Exner believes this to be the legitimate procedure in severe cases of gastric crises, but the operation, has not yet been repeated often enough to enable one to pass final judgment on it, nor has sufficient time elapsed since the

[4] Götzl, Wien. klin. Woch., 1910, vol. xxiii, No. 21.
[5] Deutsche Zeitschrift f. Chirurgie, 1911, xlviii, 1679 to 1682.

performance of the operation to determine what the ultimate results will be.

The observations made in Siding's case, in which an herpetic eruption appeared over the areas supplied by the sixth to ninth thoracic nerves make me feel all the more confident of the splanchnic origin of the crises. Furthermore, Raux,[6] in his histological researches, found that the fine nerve fibers which connect the dorsal roots to the cells in the sympathetic ganglia were partially degenerated in tabetic subjects; while the strong, medullary fibers originating in the intervertebral ganglia were not decreased to any appreciable extent. A glance at the evolution of these crises adds somewhat to the plausibility of rhizotomy in this connection, for pain and hyperesthesia are the first symptoms to appear, while the motor disorders in the form of vomiting and hypersecretion, follow probably as reflex disorders.

The first rhizotomy for the relief of gastric crises was carried out in 1908 by Förster[7] and was so successful that the operation has been repeated a number of times since. The patient, a man, aged forty-seven years, having suffered from severe crises for six years, was greatly emaciated and addicted to morphine, and no treatment had been of any avail. The laminæ of the fifth to tenth dorsal vertebræ were removed, though the dura was not opened. As no relief ensued, on the next day the dura was opened, and the sixth to tenth posterior dorsal roots were resected. The patient began to gain weight immediately, and there was no return of the crises up to the time of his death nine months later from phthisis.

In another case the patient, who was in a critical condition, had been afflicted with severe crises for ten years, and had lost over sixty pounds. He had undergone two previous abdominal operations, with no benefit. Küttner divided the sixth to eleventh posterior dorsal roots on both sides, and the patient made a complete recovery with no relapse during the two years intervening between the operation and the report.

The first case (File, No 10122), which was brought to my attention had been under the care of Dr. Kingsbury and was seen in consultation by Dr. George P. Müller, to whom I am indebted for the privilege of having operated and presenting this report. The patient, aged forty years, had been suffering for the last three years with attacks of pain and vomiting. The pain was so violent as to double him up, and the attacks recurred every four to six weeks. One year before the operation a diagnosis of cholelithiasis had been made, but an exploratory operation did not reveal any lesion of the upper abdomen. He was admitted to the University Hospital, September 6, 1911, and at that time a careful examination failed to disclose any suspicion of an organic lesion of the

[6] Neurolog. Zentralblatt, 1901, p. 27.

[7] Therapie der Gegenwart, August, 1911.

stomach, but certain well-defined symptoms of tabes dorsalis—sluggishness of the pupillary reflex, disturbances of station with eyes closed, absence of patellar and Achilles reflexes on both sides, and considerable hypotonia in flexing the thigh on the abdomen. The gastric phenomena were most pronounced, and the patient welcomed any operation which offered reasonable hope of relief.

Accordingly on September 19 I performed a rhizotomy through a unilateral or hemilaminectomy. A curved incision, beginning at the tip of the spinous process of the third thoracic vertebra and extending to the spinous process of the sixth thoracic, was made down to and through the aponeurosis. This flap was reflected and the muscles separated from the left side of the spinous processes of the fourth, fifth, and sixth thoracic vertebræ. The laminæ of the fifth, sixth, and seventh thoracic were removed with rongeur forceps and the spinal canal opened. Before the operation we decided to cut the seventh, eighth, ninth, and tenth sensory roots in the dorsal cord. The seventh root was identified as coming off the cord a little above the tip of the spinal process of the fourth thoracic vertebra. This identification was not difficult, and the plan as above outlined, was carried out, except the tenth root on the right side was left uncut, chiefly because of the difficulty in exposing it. The wound was closed with catgut sutures, a counter opening being left for drainage. The patient's condition at the end of the operation was perfectly satisfactory.

Following the operation there was some weakness in the right leg and retention of urine, but before he left the hospital he had regained vesical control and much of the power in his limb. In a recent communication the patient writes that he has been entirely relieved of the pain and vomiting, and has been gaining steadily some of the forty-five pounds he had lost since the onset of the disease three years ago. On the whole, therefore, the operation has been of the greatest benefit and more than justified itself.

Leaving out of consideration Exner's operation on the vagus nerves and Vallas and Cotte's stretching of the solar plexus, several modifications of the intradural division of the spinal roots have been proposed. For example, Guleke[8] thinks it is much simpler not to open the dura, but to divide the roots after they have left the dural sac; and Lambret,[9] after an unfortunate experience, was inclined to agree with him. Guleke operated in 2 cases according to this method, with very satisfactory results, and claims this operation can be performed with greater facility than the intradural method. But I should be inclined to think, and I believe many surgeons will uphold me in this point, that the separation of the anterior from the posterior roots after they have left the

[8] Archiv f. klin. Chirurgie, 1911, xcv, 495.
[9] Echo méd. du Nord, 1910, xiv, 589 to 591.

dural sac would be a matter of considerable difficulty, and that there would always be the additional risk of a residual palsy.

At the German Surgical Congress, March 30, 1910, Franke[10] recommended the severance of the posterior roots by avulsion of the intercostal nerves without opening the vertebral canal. His patient made a complete recovery and was able to go about his regular occupation. Von Frankl-Hochwart[11] resected the seventh, eighth, and ninth intercostal nerves in a patient suffering from gastric crises, but unfortunately only ten days intervened between the performance of the operation and the end results are not known. But little consideration, I think, should be given to the proposal of Hänel,[12] who claimed that relief may be obtained through a simple decompressive laminectomy alone, and urged that considerable time be allowed to elapse before the second stage of the operation was performed. In his case the crises disappeared after laminectomy, but unfortunately the patient died a few months later. In the experience of Küttner, Tietze, and several others, who perform the rhizotomy in two sittings, no appreciable benefit was derived from the laminectomy, though several weeks had elapsed between the two sittings.

This is not the place nor is there time to discuss at length the minor details of the operative technique, but there are a few features which I think are deserving of mention. In the first place, I do not advocate the performance of the operation in two sittings, a plan to which the German and French surgeons cling. To be sure, the grosser movements entailed in the removal of the laminæ do not fit the hand of the operator for the more delicate coördination required in the subsequent manipulation of the roots, but the advantages of the completion of the operation in one sitting so far outweigh those of the two-stage operation that unless the condition of the patient manifestly does not justify carrying the operation to its conclusion there should be no interruption. That patients in the prone position are more subject to respiratory difficulties under ether anesthesia is a matter of common knowledge, especially in rather prolonged operations; and in this connection I should like to call attention to the value of administering the anesthetic by intratracheal insufflation. To my mind the introduction of this method of administering ether is bound to have a tremendous influence in diminishing the depressing tendencies of the more serious operations, particularly where the patient is compelled to lie on the table face down, as is the case in laminectomies and operations on the posterior fossa. It is not necessary to go over the physiological grounds upon which these beneficial results are based. Suffice it to say that in my own clinical work it has relieved my mind of what once was a very disturbing factor.

[10] Centralblatt f. Chirurgie, 1910.
[11] Verhandlungen der Gesellschaft deu. Nervenärzte, 1911, p. 227.
[12] Zeitschrift f. Versicherungsmed., 1910.

As to whether the roots should be exposed by a unilateral or bilateral laminectomy is a matter which should be left to the choice of the individual operator. When the roots on both sides have to be exposed, I am rather in favor of the bilateral exposure, as it gives better access to the structures, facilitates the isolation of the roots, and thereby shortens the operation. It makes not a little difference whether one is at work in the cervical and upper thoracic or in the lower thoracic and lumbar region. The lower down in the canal the deeper are structures from the surface, and the more difficult is it to expose and differentiate the roots through a unilateral opening without traumatizing the cord unduly. In the case included in this report it so happened that I was able to accomplish my purpose by removing only one-half the laminæ. But even if the spinous processes and the whole arch of the laminæ are resected, it is surprising how little, if any, is either the strength of the back or the comfort of the patient affected.

I have been able to gather from literature the records of 30 rhizotomies for the relief of visceral crises in tabes. Of these, there were 9 complete recoveries, 16 cases in which there has been improvement, and 5 deaths. Though these results are by no means startling, yet it is exceedingly gratifying to realize that 30 per cent. have been entirely relieved and 56 per cent. partially so of a very painful complication for which hitherto there has been no source of relief other than morphine. In cases in which there has been recurrence the crises have been less severe, of shorter duration, and with longer intervals between the attacks. In the case of Bruns and Sauerbruch, in which there was a recurrence six months after the operation, the patient was able to resume his occupation as a mason, and the same was true of the 3 cases operated on by Tietze, in 1 of which a woman who had been bed ridden for two years, recovered sufficiently to be able to attend to all her household duties.

In discussing the results of the operation, a word or two should be said about the mortality and the recurrences. As for the mortality, it should be borne in mind that in a number of instances the patients were anything but fit subjects for operative intervention. Many are exhausted by pain and suffering, many addicted to the morphine habit, always an undesirable situation to deal with, others again are subjects of toxemia from infection of the urinary tract, in fact, 2 of the series died as a result of cystitis. In order that the operation should not meet with disapprobation because of the mortality incident to it, it behooves neurologists and surgeons alike to exercise the greatest discretion in the selection of cases and to advise operation, if at all, in the earliest stages before the patients are rendered unfit by complications above mentioned for an operation, which, though involving no extraordinary risks, must be rated as a major surgical procedure.

In considering the variable results following root resection, attention should be drawn to the experimental work of Kidd[13] who has already collected a large amount of evidence, surgical, experimental, histological, and embryological, which he thinks leads to the inevitable conclusion that afferent fibers in some cases algetic, in others reflex, exist in the spinal ventral roots of man and many other vertebrates. And he even goes so far as to advocate the division of the ventral as well as the dorsal roots except in the case of the third and fourth cervical roots. The resulting disability would be preferred, he believes, to the continuance of pain.

That the section of a given number of roots should in some cases be attended with complete recovery, in others with only partial recovery, and again in others should be followed by recurrence, is a matter which at once provokes an interesting discussion. Förster attributes the unsatisfactory results to the fact that an insufficient number of nerves have been cut, as the sympathetic nerve fibers originating in the stomach and intestines are very numerous. He therefore recommends that the greatest possible number of nerves be divided, including the fifth and sixth, and eleventh and twelfth, as well as the seventh to ninth, which alone were at first thought necessary. This theory would seem to be substantiated by one of Guleke's[14] cases, in which a relapse occurred after the resection of the seventh to ninth dorsal roots, but when the patient has been subjected to a second operation, at which the tenth and eleventh roots also were divided, there was no further trouble. It may be that Förster's explanation will solve the problem. At least I have found that in many instances recorded as recurrences the pain did not recur in the stomach at all, but was referred to the intestines, that is, to the lower rather than the upper abdomen. It would seem more than plausible, therefore, that we should be able to prevent the subsequent development of crises in the intestinal tract, improperly designated as recurrence, by cutting the tenth and eleventh thoracic, in addition to the roots immediately above. Whether it is necessary in the light of our present knowledge of the nervous supply of the stomach to section the two roots above the seventh—namely, the fifth and sixth—is a matter which can be determined only by subsequent observations and further experience.

If it be true that in some cases the gastric crises of tabes have their origin in some form of irritation of the pneumogastric nerves, it goes without saying that a rhizotomy of the dorsal roots in these cases will be of no benefit whatsoever. The fact that in none of the recorded cases did the patients fail to derive some relief from section of the dorsal roots would seem to controvert this theory.

[13] British Med. Jour., August 19, 1911.
[14] Archiv klin. Chir., 1911, xcv, 495.

However, if it be true, as I understand to be the case, that neurologists recognize clinically an exceptional type in which the crises are of pneumogastric origin, there should be no hyperesthesia in the cutaneous distribution of the dorsal roots and no increase in the epigastric reflex; and according to the observations of Head, there should be hyperesthesia in the temporal and parietal regions as the sensory fibers of the trigeminus occupy the same segment as those of the vagus. If this clinical differentiation is possible, there should be no difficulty in excluding those cases in which dorsal root resection is contraindicated.

The time has come when those who are interested in the development of surgery in the field of neurology should come to some conclusion as regards the propriety of this comparatively new operation, technically known as rhizotomy, with its varied applications. Laminectomy as an operation has lost many of the terrors with which it was associated in the minds of the past generation. I have had to open the dural sac on a number of occasions for a great variety of conditions, with the loss of only 2 cases—1 a multiple sarcoma of the cord, and the other a root resection in an imbecile child; the death in the former instance was attributed to exhaustion, and in the latter to a very peculiar train of events which did not seem to bear directly on the character of the operation. Personally, I am quite prepared to advocate in most positive terms rhizotomy as a means of relieving pain in suitable cases and where other measures have failed: (1) Because it is based on a sound physiological basis, and (2) because it has been followed by gratifying results in not an inconsiderable percentage of cases.

A CASE OF ALKAPTONURIA.

By Helen Baldwin, M.D.,
NEW YORK CITY.

(From the Herter Laboratory, New York City.)

As alkaptonuria is a congenital anomaly of metabolism rather than a disease its interest must lie mainly in the indications which it may give as to the development of metabolic processes in fetal life or as to the normal oxidation in those substances whose abnormal catabolism it represents. The patients having alkaptonuria present no characteristic symptoms. The only diagnostic alteration in their metabolism which has been discovered is in their failure to normally burn tyrosin and phenylalanin. These sub-

stances, whether they have been taken in the food or built up in the tissues or given experimentally, are converted into homogentisic acid, which is excreted unchanged in the urine. As the cause of this condition is still unknown, and as relatively few cases have been reported[1] (about 60 in all), it has seemed well to add this record to those which have been published.

Mrs. A. J., a widow, aged thirty-one years, applied for treatment November 1, 1910, suffering from vague rheumatoid pains in her back and neck, accompanied by a general feeling of weakness. Ten years ago she was told by a physician she had diabetes.

Family History. The patient's father and mother were born in Germany. There is no consanguinity in the families of her parents. No history can be obtained of any of her family having urine which darkened on standing or which stained the clothing. Specimens of urine from 9 of her relatives have been examined in connection with this study of her case. None of these contained homogentisic acid. There is a family tendency toward diabetes. One sister and a nephew have a distinct reaction for sugar in the urine. The patient's mother, another sister, a niece, and another nephew had a trace of sugar in the urine. The urine from her father and from two of her sisters was normal. In all these cases of glycosuria, sugar was found both by fermentation and by Fehling's method.

Personal History. When the patient was aged about one year, her mother first noticed that her diapers were stained by the urine. This was noted more as she grew older, when the urine stained the clothing a "red, brick red or maroon" color. She was well throughout her childhood. Menstruation began at seventeen years. The menstrual blood was sometimes dark, almost black in color; sometimes it was bright red; this darkening of the menstrual blood was probably from admixture with urine. She was married ten years ago. She was never pregnant. Three years ago her appendix and a cyst of the right ovary were removed, and as she had severe backache and metrorrhagia following the operation the left ovary and a part of the uterus were removed later. She has frequent pain in the left eye, the left side of the head, and extending up the left side of the neck. She has frequent numbness in the fingers of the left hand. She is also subject to pain and stiffness in the lumbar region, so that she has to be helped in rising from a recumbent position when she wakes. Some days she has great thirst. The amount of urine varies greatly, and at times she passes excessively large amounts. She sweats freely all the time. Her mentality is normal, but she is neurotic in temperament.

[1] See Garrod, Inborn Errors of Metabolism, 1909, and Fromberg, Neure Forschungen auf dem Gebiet der Alkaptonurie. Biochem. Centralbl., 1908–1909, viii, 1–9.

PHYSICAL EXAMINATION. The patient is a tall, well-nourished woman, with a dark complexion and black hair. Her usual weight is 125 pounds. The sclerotic coats of the eyes have a grayish tint (ochronosis). There is one small dark spot in the cartilage of the left ear, otherwise the cartilages as well as the finger nails are normal in color. The thyroid gland is slightly enlarged. The heart, lungs, and abdominal organs appear normal. The systolic blood pressure is 120 mm. in both radial arteries. Her pulse rate is 84.

URINARY ANALYSIS. The urine gives the characteristic reactions found in cases of alkaptonuria, which are due to the presence of homogentisic acid, which is a powerful reducing agent and turns brown when it is oxidized. The color of the freshly voided urine is pale yellow. It soon assumes a brownish tint, which slowly darkens until the urine becomes nearly black. When an alkali is added the surface exposed to the air quickly becomes brown and the darkening of the entire specimen is hastened. When ammonia is added to the urine, and it is allowed to stand, it becomes a deep brownish-red color. When the urine is mixed with Fehling's solution the blue color is first changed to green before heating, then it gradually assumes a brown color from the presence of the alkali. On boiling, Fehling's solution is reduced with the formation of a reddish-brown precipitate. The urine rapidly reduces an ammoniacal solution of silver nitrate even when no heat is applied. On heating the urine with Nylander's reagent there is no reduction of the bismuth. There is no yeast fermentation, and the urine is optically inactive. On adding dilute ferric chloride solution drop by drop an evanescent bluish-green color is produced. Homogentisic acid was separated out from the urine and was identified by Dr. H. D. Dakin,[2] who has reported some experiments in metabolism which he made upon this patient.

General examination of urine, May 12, 1911: Volume, 1140 c.c. in twenty-four hours; color, light yellow; specific gravity, 1021; albumin, negative; indican, slight; indol-acetic acid, slight; *p*-dimethylaminobenzaldehyde reaction, slight; acetone, trace; phenol, marked reaction; sugar, negative.

NITROGEN EXCRETION AND NITROGEN PARTITION. The first specimens of urine were collected when the patient was on a general mixed diet of her own choosing; these showed an excessive nitrogen excretion and an abnormally large volume. Thus on November 22, 1910, the volume measured 4260 c.c., with the total nitrogen 36.8 grams. November 29 the volume was 2900 c.c. and the nitrogen 27.3 grams. The patient was told she was taking too much nitrogenous food, and after that the diet became more normal.

[2] Jour. Biol. Chem., 1911, ix, 151.

TABLE I.—Nitrogen Partition.

	March 28, 1911.		May 12, 1911.	
	Grams.	Per cent. of Total N.	Grams.	Per cent. of Total N.
Total nitrogen	21.05	.....	10.81	
Urea nitrogen	19.52	92.73	9.74	90.1
Ammonia nitrogen	0.52	2.47	0.43	4.0
Purin nitrogen	0.25	1.19	0.22	2.0
Creatinin nitrogen	0.33	1.57	0.37	3.4
Hippuric acid nitrogen	0.34	1.61	0.03	0.3
Undetermined nitrogen	0.09	0.43	0.02	0.2

The nitrogen partition[3] was made on two specimens, each representing an average of two days (Table I). The percentage of the various forms of nitrogen in these analyses did not deviate from the normal. The percentage of urea is high showing that there was a rather unusually complete digestion and utilization of the nitrogen of the food. The ammonia excretion is normal or slightly high for normal but not as high as one would expect with so large an amount of homogentisic acid in the urine. This also has been noted by Schumm,[4] who found only from 5.05 to 6.89 per cent. of nitrogen of ammonia in the urine of his patient. The nitrogen of ammonia was determined on the following days:

January 9, 1911	0.82 grams	4.9 per cent.
January 25, 1911	0.87 grams	4.7 per cent.
March 28, 1911	0.52 grams	2.5 per cent.
May 12, 1911	0.43 grams	4.0 per cent.
September 7, 1911	0.66 grams	3.7 per cent.

The daily excretion of uric acid in the case of this patient varied very widely. In the specimens on which the nitrogen partition was made the amount of uric acid was normal. In a collection made for two days, January 9 and 10, 1911, the daily average was only 0.0087 gram., the nitrogen of uric acid being 0.017 per cent. of the total nitrogen. Wide variations in the amount of uric acid

[3] Methods: The homogentisic acid in the urine renders inaccurate a number of the usual methods of urinary analysis. The following methods were used in this case. Duplicate analyses were made in the quantitative determinations.

Total nitrogen: Kjeldahl's method.

Urea nitrogen: Morner und Sjöquist's method (Neubauer und Vogel [Huppert], Analyse des Harns).

Ammonia nitrogen, uric acid nitrogen, creatinin nitrogen, and indican. According to Folin (Amer. Jour. Physiol., 1905, xiii, 45), before determining the creatinin the homogentisic acid must be removed by continuous extraction with ether after acidifying with a mineral acid. For the precipitation of the uric acid a small narrow-necked (Ehrlenmeyer), well-stoppered flask was used. In making the ammonia determinations, rapid suction was continued for four hours.

Remaining purin nitrogen after removal of uric acid. Method of Krüger und Schmidt (Zeitsch. f. physiol. Chemie, 1905, xlv, 1); modified by Benedict (Jour. Biolog. Chem., 1909, vii, 27).

Sulphur: Benedict's method (Jour. Biolog. Chem., 1909, vi, 363).

Sulphates: Folin's method (Jour. Biolog. Chem., 1906, i, 131).

[4] Münch. med. Woch., 1904, p. 1599.

excreted have been reported by many writers, the amount having been reported as abnormally low by Embden,[5] Stange,[6] and Ogden.[7]

SULPHUR PARTITION. The sulphur partition was determined for five days (Table II). The sulphuric acid combining with aromatic bodies varied widely on the different days, three of the specimens having a low ratio for the aromatic sulphuric acid and one a relatively high ratio $\left(\frac{H_2SO_4I}{H_2SO_4E} = 7.3\right)$. The neutral sulphur in the urine is normal in amount although the hydrogen sulphide in the feces is above the normal.

TABLE II.—Sulphur Partition.

Date.	Total S as H_2SO_4.	Total oxidized, H_2SO_4.	Inorganic, H_2SO_4.		Ethereal, H_2SO_4.		Neutral, H_2SO_4.		Ratio: $\frac{\text{Inorganic, } H_2SO_4}{\text{Ethereal, } H_2SO_4}$.
	Grams.	Grams.	Grams.	Per cent.	Grams.	Per cent.	Grams.	Per cent.	
January 9, 1911 . .	3.895	3.469	3.330	85.5	0.139	3.6	0.426	10.9	24.0
January 25, 1911 . .	3.678	3.302	3.200	87.0	0.102	2.8	0.376	10.2	31.4
March 28, 1911 . .	3.143	2.771	2.439	77.6	0.332	10.6	0.372	11.8	7.3
May 12, 1911 . . .	2.313	2.016	1.858	80.3	0.158	6.8	0.297	12.9	11.8
September 7, 1911 .	4.094	3.538	3.385	82.7	0.153	3.7	0.556	13.6	22.1

AROMATIC COMPOUNDS. In the oxidation of both tyrosin and phenylalanin, in cases of alkaptonuria, the benzene ring is not broken down, but instead homogentisic acid is formed which is itself an aromatic compound. As the essential anomaly in this condition lies in the imperfect oxidation of two aromatic bodies, the behavior of all aromatic compounds becomes of special interest. In the present case tests were made in the urine for the following aromatic bodies: Indican, phenol, total ethereal sulphates, hippuric acid, the aromatic oxyacids, and idolacetic acid. The specimens were also tested with the *p*-dimethylaminobenzaldehyde reagent, which reacts with certain aromatic as well as other substances.

There were wide variations in the ratio between the aromatic and preformed sulphates, as has been noted by other observers (Table II). Indican was present in small amounts in some of the specimens and negative in others. The qualitative test for phenol in the acid distillate was sometimes negative and sometimes gave a marked reaction. Hippuric acid was present in normal amounts.

[5] Zeitsch. f. physiol. Chem., 1893, xvii, 182.
[6] Virchow's Archiv, 1896, cxlvi, 86.
[7] Zeitsch. f. physiol. Chem., 1895, xx, 279.

The aromatic oxyacids and indolacetic acid were present in traces. The *p*-dimethylaminobenzaldehyde reaction was very slight. It is thus seen that there was no characteristic variation in the amount of any of these aromatic compounds.

Sugar Tolerance. The urine of this patient as stated above was found to be free from sugar; that is, there was no yeast fermentation and the urine was optically inactive. The sugar tolerance of the patient was tested. One hundred and fifty grams of cane sugar were given and the urine collected for twelve hours from the time of taking the sugar. The urine by fermentation was found to contain a distinct trace of sugar. One hundred and twenty grams of sugar were then given, and the urine collected for twelve hours was found to contain 7.8 grams of sugar. Again, 132 grams of sugar were given, and during the next six hours, 0.3 gram of sugar was found in the urine. It is thus seen that the tolerance for sugar is nearly normal, but it is at times a little low.

Feces, April 18, 1911: Color, dark; reaction, alkaline.

Microscopic Examination: Vegetable fibers, vegetable spirals, oil droplets, starch granules, no meat fibers found.

Bacteriological Examination: Gram-stained smears from the feces appear normal; Gram-negative bacilli are the prevailing form of bacteria. Hydrogen sulphide in the moist feces, 0.032 per cent.

Blood Examination, August 29, 1911: Red blood corpuscles, 3,152,000; leukocytes, 2000; hemoglobin, 78 per cent.; polymorphonuclear cells, 60 per cent.; small lymphocytes, 34 per cent.; large lymphocytes, 4 per cent.; transitional forms, 1 per cent.; eosinophiles, 1 per cent.

The blood coagulates more rapidly than is normal. In a capillary tube, coagulation begins within one and three-quarters minutes, and is complete in two minutes.

The perspiration and ear wax do not give any reaction for homogentisic acid.

The classical symptoms of alkaptonuria which have been noted in this case are the constant presence in the urine of homogentisic acid, the darkening of the sclerotic coats of the eyes and slight darkening of the cartilage of the ear (ochronosis), and the local irritation of the strongly acid urine. Other less characteristic symptoms noted in this case which have been reported in some cases of alkaptonuria are a general weakness, a neurotic disposition, a tendency to rheumatoid pains, and an irritation of the bladder causing an increase of bladder cells and of leukocytes in the urine. Other unusual symptoms of this patient are a rapid coagulation of the blood and a slightly low tolerance for sugar, with a family history of diabetes. It may be worthy of note that the patient is from a German family. The most of the cases have been reported by physicians in Germany, and of those reported from other countries several have been German.

REVIEWS

THE ANATOMY OF THE HUMAN EYE AS ILLUSTRATED BY ENLARGED STEREOSCOPIC PHOTOGRAPHS. By ARTHUR THOMSON, M.A., M.B., F.R.C.S., Professor of Human Anatomy in the University of Oxford. Pp. 131; 67 stereoscopic photographs. London: Henry Frowde, 1912.

THIS contribution to the gross anatomy of the human eye consists of a series of sixty-seven stereoscopic photographs, under a magnification of from two to three diameters, accompanied by a small volume of descriptive text. Although the application of stereoscopic photography to the display of anatomical structures is no longer a novelty, it has seldom been used to better advantage than in the present instance. This satisfactory result, however, depends by no means solely on the stereoscopic effect, but on the combination of the latter with an enlargement sufficient to exhibit details and relations, which are inadequately seen with the unaided eye. Many of the pictures are telling examples of the value of hand-glass anatomy—a method of study too much neglected, now that the microtome and microscope stand ever ready.

The illustrations comprise five groups: (*a*) anteroposterior sections of the eye; (*b*) dissections of the eye from the front; (*c*) anterior half of the eye seen from behind; (*d*) the lens; (*e*) posterior half of the eye.

The first group offers most instructive views of the fibrous tunic, with its variations in thickness and the relations of the sulcus scleræ to the sulcus circularis corneæ. Admirable views are afforded also of the suspensory apparatus of the lens and of the ora serrata; likewise of the optic nerve and papilla. The sections of fetal eyes exhibit the thick cornea, the spherical lens, and the redundant retina, as well as the hyaloid artery.

The dissections of the eye from the front supply instructive pictures of the iris and of the lens, with its striæ shimmering through the pupil. One of the most interesting preparations was made by removing half of the iris, after the sclera and cornea had been cut away, and thus exposing the posterior chamber and its posterior wall. In other preparations the entire iris has been removed, with the cornea and part of the sclera, in this way displaying the complete ring of the suspensory ligament attached to the lens. By

photographing with a combination of transmitted and reflected light, the details of the zonule of Zinn are shown with unusual clearness, the radially disposed suspensory fibers, passing from the inner surface of the ciliary body to the circumference of the lens, appearing with great distinctness.

The ciliary processes, orbiculus ciliaris, and ora serrata are strikingly shown in several photographs of the anterior half of the eye, taken from behind. The quite regular alternation of the larger and smaller ciliary processes is emphasized, as well as the larger number of the folds, from sixty-eight to eighty, than the usually assumed quota. Of the views of the posterior segment of the eye, several are of particular interest, as they show not only the optic disk, physiological excavation, and retinal vessels, but also the macula and the fovea.

The sixty odd pages of text accompanying the plates, although arranged to call attention to the many interesting details to be seen in the photographs, are much more than a mere description of the illustrations, constituting, as they do, an excellent synopsis of the gross anatomy of the human eye, well meriting a careful perusal. A series of leadered outline figures, giving in detail names and relations, forms an adequate key for the identification of the structures shown in each photograph.

The plates, as photographs, are, with few exceptions, excellent, not a few being exceptionally sharp and clear. The difficulty of obtaining such results will be appreciated best by those having had actual experience in photographing preparations in fluid and under magnification.

Professor Thomson has supplied the means of acquiring an understanding of the eye, which should be welcomed not only by students of anatomy, but also by surgeons concerned with the delicate structures of the organ of vision. G. A. P.

THE PRACTITIONER'S VISITING LIST FOR 1913. Pp. 192; 3 illustrations. Philadelphia and New York: Lea & Febiger.

ONE of the most useful aids to the busy physician that has recently come to our notice is *The Practitioner's Visiting List* for 1913. With such a well-arranged and convenient little book ever ready in his pocket the most hard pressed of practitioners should easily be able to keep accurate account of his visits. The book is issued in several styles so as to meet the requirements of even the largest practice.

A valuable feature of this Visiting List is the accompanying text, which contains the information that a doctor continually

needs: for example, a scheme of dentition; tables of weights and measures; a diagnostic table of eruptive fevers; a list of incompatibles, poisons, antidotes, a table of doses, etc.

The excellence of this little book makes it evident that the issue for 1913 will receive the same hearty welcome from physicians throughout the country that has uniformly been accorded the preceding twenty-eight issues. G. M. P.

PLEURISY. By ALEX. JAMES, M.D., Consulting Physician to the Edinburgh Royal Infirmary. Pp. 240; 4 illustrations, 4 clinical charts, and 19 diagrams. New York: William Wood & Co.

THIS book, which the author states is the outcome of thirty years' experience in hospital and private practice, presents his views on a subject about which he is well qualified to speak, and which he has abundantly illustrated by case-reports. Besides being an able treatise, it has, therefore, the added value of emphasizing in a clear direct style those ideas which are particularly his. He states in the preface: "It may be at once remarked that any reader who considers full reference to medical literature essential in a medical book need not read farther. . . . Rather has it been my endeavor to hand on the broad general truths regarding this disease which the generation to which I belong has inherited, along with what little in the way of illustration, explanation, and augmentation my experience and reading seem to me to be able to add."

The first three of the fourteen chapters discuss the etiology of pleurisy. Then follows a detailed description of pleural effusions, empyema, pleurisy associated with malignant growths, and streptothrix and leptothrix infections. A chapter on treatment closes the work. The consideration of empyema occupies nearly half of the book, there is a chapter on its natural methods of cure, on the relation of empyema to bronchiectatic cavities, on its unusual localizations, on fetid effusions, and on pulsating and phthisical empyemas.

What most attracts interest in the book is the handling of the mechanical problems connected with effusions, the arguments being ingenious, and made lucid by a liberal use of diagrams. Dr. James does not share the generally accepted view that the heart is displaced by the pressure of fluid, believing on the contrary, that when the lung on the affected side relaxes, the elastic traction of the sound lung pulls the heart to the opposite side. His argument is supported by experiment. Of similar interest is the consideration of the bulging and non-bulging of intercostal spaces, of the formation of the S-shaped curve, and particularly of the mode of formation

of bronchiectatic cavities. To the explanations for pulsationg empyema already extant, he adds another and very plausible one, supported by a case history and autopsy.

In instances of the delayed reabsorption of serous effusion he strongly advocates allowing the patient to be guided by his own feelings about getting up, putting him to bed only on a return of fever or pain, a practice which has been followed also in cardiac cases with benefit and comfort to the patient. In the treatment of empyema, one is rather surprised at the frequent mention of chloroform, and is led to assume that the use of local anesthesia for this condition is not so common in Edinburgh as it is with us. Evidently "red meat and red wine" is a by-word there, for it is mentioned often in the treatment of the phthisical.

James' *Pleurisy* is interesting reading. It is characterized throughout by its directness and good sense, and its ideas are stimulating, whether one accepts or diagrees with them. H. G. S.

INFANT FEEDING. By CLIFFORD G. GRULEE, A.M., M.D., Assistant Professor of Pediatrics, Rush Medical College, Chicago. Pp. 295; 29 illustrations, and 8 original colored plates. Philadelphia: W. B. Saunders Co., 1912.

THE author considers the subject under four heads: (1) Principles of nutrition including anatomy, physiology, and metabolism; (2) breast feeding; (3) artificial feeding; (4) nutrition in other conditions commonly found in infancy.

Judged by the standards recently set by Continental pediatricians he has succeeded in the difficult task of effectively covering the broad field of the infants' nutrition. This difficulty is greatly increased by the uncertainty which is felt by most American observers as to the underlying as well as active causes of many of the nutritional and gastrointestinal disturbances in infancy.

The author accepts, in large part, the teachings of Finkelstein and Mayer, and divides the gastro-enteric disorders as follows: Weight disturbances (chiefly fat intolerance), dyspepsia (duodenal indigestions, fatty diarrhea), decomposition (marasmus), intoxication (summer diarrhea, ileo-colitis, cholera infantum, dysentery).

The importance of Finkelstein's teaching is generally admitted in America, but it is questionable whether or not we are prepared to agree absolutely with the statement "that the primary cause of the intoxications (see synonyms) is a dietetic one and that the specific action of the pathogenic bacteria is secondary to the primary nutritional defect." If this be true, we must be prepared to hear that true cholera and amebic dysentery are due to dietary

indiscretions, or that the pneumococcus bears no important etiologic relation to pneumonia, because its habitat frequently is found in the air-passages of well persons. Fortunately for the patient, the uncertainties as to etiology do not materially affect the dietetic treatment of the intoxications and the advice on this head is sound and practical, while the great danger of "doing too much" is emphasized by the simplicity and saneness of the advice with regard to drugs and other therapeutic measure. The book will prove to be a most useful one to the student and general practitioner.

J. C. G.

A TEXT-BOOK OF OBSTETRICS. By J. WHITRIDGE WILLIAMS, M.D., Professor of Obstetrics, Johns Hopkins University. Third edition; pp. 946. New York and London: D. Appleton & Company, 1912.

THIS book is so well and so favorably known that an extended review is unnecessary. It has been thoroughly revised and brought up-to-date, and although the author states in his preface that he has been criticised for the inclusion of a list of references at the end of each chapter, it is hard to see how such criticism can be justified. Such an arrangement must be of enormuous help to the student and particularly to the busy practitioner, and in our opinion is heartily to be commended. Two criticisms only suggest themselves: The position of the patient in Fig. 310, p. 323, illustrating the proper position for delivery, involves more exposure than is desirable in most cases and does not allow the same facility in protecting the perineum from injury that is afforded by delivery upon the side; and, secondly, nearly all the illustrations of examinations, obstetric operations, etc., depict an operator with bare hands without rubber gloves, an omission that should be corrected in future editions. The illustrations are numorous, exceedingly well executed, really illustrate what they are intended to show, and as an example of the book-maker's art it is hard to see how the volume could be excelled. J. C. H.

A COLLECTION OF PAPERS PUBLISHED PREVIOUS TO 1909. By WILLIAM J. MAYO and CHARLES H. MAYO. Volume I, pp. 498; 46 illustrations. Volume II, pp. 591; 25 illustrations. Philadelphia and London: W. B. Saunders Company, 1912.

DOUBLE frontispieces, showing the two authors as recent graduates and as mature surgeons, are prefixed to these volumes which contain a vast miscellany of reprints on all sorts of surgical subjects.

The earliest papers date from 1884. Some are of only ephemeral interest, and a few of no interest at all; most of them, however, are well worthy of preservation in the excellent form in which they are presented by the comptetent editor, Mrs. M. H. Mellish.

The first volume contains mostly papers dealing with abdominal surgery. The second volume, besides numerous articles on the surgery of the intestines, includes such various topics as extra-uterine pregnancy, skin-grafting, aneurysm, mastoid abscess, infantile spinal paralysis, brain cysts, fractures, and infections of joints. There are also several "travelogues," and numerous occasional addresses.

All of these articles presumably have long ago reached the audiences for which they were intended, and no further comment is required. The Mayo brothers have passed a busy life, observing keenly, studying industriously, and teaching themselves and others most indefatigably. To see the present volumes as mementoes of work accomplished surely brings its own reward. A. P. C. A.

TRÉPANATION NÉOLITHIQUE, TRÉPANATION PRÉ-COLOMBIENNE, TRÉPANATION DES KABYLES, TRÉPANATION TRADITIONELLE. Par le DR. LUCAS-CHAMPIONNIÈRE, Membre de l'Institut (Académie des Sciences), Chirurgien Honoraire de l'Hôtel Dieu, Membre de l'Académie de Médecine, etc. Pp. 136; 32 illustrations. Paris: G. Steinheil, 1912.

LUCAS-CHAMPIONNIÈRE was a pioneer in head surgery. At the commencement of his career, in the sixties and seventies of the last century, the operation of trephining had fallen into great disrepute. He not only undertook to revive it, under antiseptic precautions, and to guide his interventions by the newly established methods of cerebral localization, but he developed the theory of *decompression*, which has later been widely accepted. Now that the passage of years has enabled him to retire from active practice, he employs his time, with characteristic indefatigability, in historical researches such as that now before us.

Prehistoric trepanning, as it is called, was established as a fact in 1868, when certain neolithic skulls were found in France. These bore oval openings in the calvaria, sometimes of amazing size; and the margins of these openings had become cicatrized, showing that the patients had long survived the operations. What is more, the buttons of bone removed from these skulls, and carefully preserved, were found also. Trepanning is known also to have been practised by the prehistoric inhabitants of Peru, and by some tribes of North American Indians, before the age of Columbus. Lucas-Champion-

nière gives here not only a description, with photographic plates, of the most important of these neolithic skulls; but he also argues that the therapeutic effects of decompression, as we know them today, must have been well appreciated by these prehistoric peoples. He compares these facts and specimens with the trepanning practised in modern times by some of the savage or semi-civilized races such as the Kabyles of Northern Africa, the mountaineers of Daghistan and of Montenegro, and in some of the islands of Polynesia.

It is an interesting volume, which forms the first part of a proposed historical study of the operation of trephining; the second part will be welcome when it appears. A. P. C. A.

FURTHER RESEARCHES INTO INDUCED CELL REPRODUCTION AND CANCER. By H. C. ROSS. Pp. 63; 5 colored illustrations. Philadelphia and London: P. Blakiston's Son & Company and John Murray.

THE book consists of a ten-page preface by H. C. Ross, in answer to criticisms of his earlier work, and five papers by H. C. Ross, J. W. Cropper, and E. H. Ross. The first paper is a further study of the so-called "auxetics" and "kinetics" described in Induced Cell Reproduction and Cancer; the second describes a method for making fixed films of cells studied by Ross' "in vitro" method; the third describes the application of "auxetics" and "kinetics" to cells floating in a fluid medium rather than on a jelly film; the fourth describes an investigation of the gasworks pitch industries and cancer (abridged from the *British Medical Journal*, April 15, 1911); and the fifth describes the action of auxetics on erythrocytes.

What already has been said in reference to *Induced Cell Reproduction and Cancer* (AMER. JOUR. MED. SCI., 1911, cxli, 895) applies equally to the first four of these studies. The fifth paper, by a new worker in this field, E. H. Ross, describes the application of the principles and methods of H. C. Ross to the study of division in mammalian erythrocytes. The author considers the nucleated red cell and granular erythrocyte to be of the same class, but appears to have been more successful in his experiments with the latter cell. The cell may divide into a variable number of daughter cells, depending on the size of the parent cell. Within certain limits, it seems that the further the conditions of the experiment are removed from those of normal adult circulating blood, the more likely is it to be successful.

The book, throughout, shows the same deficiency in detailed report of individual experiments, the same general type of illy founded conclusions, the same disregard of other work in physical biology, and the same diffuse pedantic style of presentation noted in its predecessor. H. T. K.

COLLECTED PAPERS BY THE STAFF OF ST. MARY'S HOSPITAL, MAYO CLINIC, ROCHESTER, MINNESOTA, 1911. Pp. 603; 250 illustrations. Philadelphia and London: W. B. Saunders Company, 1912.

THERE are twenty-three contributors to this volume, of which Mrs. M. H. Mellish is the capable editor. Nearly two hundred pages are occupied by papers dealing with the surgery of the alimentary canal, including nearly every subject of importance from carcinoma of the lips and tumors of the vomer to intestinal parasites and diverticulitis of the rectum. It is rather stretching a point, however, to include "Hodgkin's Disease" and "Sarcoma of the Cervical Glands" among lesions of the alimentary tract. Genito-urinary subjects occupy more than two hundred pages; and it is again somewhat of a shock to find carcinoma of the breast classed here with surgery of the prostate, ureteral calculi, and tuberculosis of the kidneys. The temptation even for abdominal surgeons to have their say on the burning question of the day—the operative treatment of fractures—proves too strong to resist, and we find two papers dealing with this subject. The results secured do not appear to have been particularly brilliant. It is interesting to be told that Mr. Lane employs wooden screws to hold his steel plates in position. Perhaps we may expect in next year's volume accounts of arthroplasties, if not indeed disquisitions on the pathology and treatment of congenital dislocations. "Nil intentatum nostri liquere poëtæ." A. P. C. A.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, WASHINGTON UNIVERSITY, ST. LOUIS, MISSOURI.

The Wassermann Reaction in the Rabbit.—In 1908 Sachs and Altmann found that syphilitic sera, which gave a negative Wassermann reaction in the inactivated state, frequently exhibited a strongly positive reaction when active. The fact that certain normal sera also reacted positively prevented the utilization of this fact in a diagnostic way. L. HALBERSTAEDTER (*Berlin. klin. Woch.*, 1912, xlix, 594) has made the interesting observation that the conditions are exactly reversed in the rabbit. He finds that the serum of most normal rabbits, when inactivated, gives the Wassermann reaction. In the fresh, active state, the sera of normal rabbits give a negative reaction almost without exception. Occasionally there is slight inhibition of hemolysis, but never a well marked positive reaction. The serum of rabbits infected with dourine, however, gives a positive reaction. The possibility is, therefore, apparently present of finding specific immunity reactions in the rabbit through the examination of sera in the active state. The observations appear to be of considerable importance in view of the extensive experimental researches, which are being made at the present time on lues.

The Histological Disappearance of Skin Syphilides under Salvarsan.—ROHRBACH (*Münch. med. Woch.*, 1912, lix, 967) has made histological studies of various skin lesions of syphilis under the influence of treatment, particularly with salvarsan. He finds that the specific infiltrations persist for some time, though the diffuse leukocytic infiltrations disappear more rapidly. The morphological picture and the extent of the plasma cell infiltration furnish a good indication as to the more

or less successful destruction of the spirochetes. The early institution of treatment and the administration of salvarsan at frequent intervals markedly influence the quality and rapidity of disappearance of the infiltrations. Endarteritic changes are strikingly affected by treatment. Following salvarsan, the elastic fibers undergo further injury, and may disappear entirely; in other words, elastic tissue is less affected by the living spirochetes than by their endotoxins. In view of the long duration of the infiltrations in many cases, it would appear to be rational treatment to combine inunctions with the salvarsan.

The Histological Structure of Syphilitic Lesions in the Rabbit.—UHLENHUTH, P. MULZER, and M. KOCH (*Deutsch. med. Woch.*, 1912, xxxviii, 1079) have made a histological study of the lesions in syphilitic rabbits. They summarize their findings as follows: Regardless of the source of the material, the nature of the lesions produced is practically identical. There are formed granulations or granulation tumors arising from the mononuclear lymphoid cells; in the central zone there appears very early a tissue suggesting embryonic connective tissue, which the authors designate mucinous degenerated connective tissue. The lymphoid infiltration is usually diffuse, less often in the form of a nodule; in the latter epithelioid cells may be found. Among the lymphoid cells numerous plasma cells are found, and also eosinophile cells. In certain instances plasma cells were so abundant that they predominated. Giant cells were observed in only one case; they were situated in the mucinous degenerated connective tissue. They were quite small and corresponded to the so-called Langhans type. Miliary foci of necrosis, such as are found in the liver and adrenals of newborn infants, were seen frequently, usually in the mucinous degenerated connective tissue. Perivascular lymphoid infiltrations were not uncommon, whereas partial or complete obliteration of the vessels was noted only a few times. In some cases cells filled with fat droplets were numerous at the edge of the lymphoid infiltration next to the mucinous degenerated tissue. The disappearance of the testicular canaliculi was analogous to the condition observed in human syphilitic orchitis, except for the scarcity of elastic tissue fibers in the rabbit. The richness of the lesions in spirochetes is striking and finds its parallel in human congenital syphilis. The lesions in the rabbit resemble those of congenital lues rather than the acquired disease of adults in other respects. There is an absence of extensive necrosis or caseation in the central area of the granulation tumors. The authors consider the mucinous degeneration of the connective tissue seen in the rabbit as a specific reaction of the rabbit—the equivalent of the necrosis or caseation found in human cases.

Recent Modifications of the Romanowsky Stain.—S. SZÉESI (*Deutsch. med. Woch.*, 1912, xxxviii, 1082) reviews some of the more recent modifications of the Romanowsky stain, and concludes that the panoptical method of Pappenheim, which follows, is the best. (*a*) The dry films are fixed in May-Grunwald's staining solution three minutes. (The stain is a modified Jenner's stain, which is dissolved in methyl alcohol.) (*b*) Next add an equal quantity of distilled water, and

stain one minute. (*c*) Pour off the stain without washing, and then treat the specimen with freshly prepared aqueous Giemsa's solution fifteen minutes. (*d*) Wash thoroughly in water. (*e*) Blot dry. (Avoid drying over the flame, since the azure staining is injured). (*f*) Mount in neutral Canada balsam. The erythrocytes are rose colored, polychromatophilic red cells bluish violet, basophilic granulation blue, nuclear particles reddish violet. The nuclei of leukocytes are violet, often reddish violet. The bodies of lymphocytes are light blue, Neutrophilic granules take a brownish color, and are remarkably sharp and distinct. The eosinophilic granules are red, mast cell granules ultramarine blue, azure granules purplish red. The technique is simple, and the results almost uniformly good.

Clinical Experience with Neosalvarsan.—A. STÜHMER (*Deutsch. med. Woch.*, 1912, xxxviii, 983) has had the opportunity of using neosalvarsan in a variety of luetics at various stages of the disease. As with salvarsan, he began by employing intramuscular injections of the drug, but soon abandoned this method of administration for the intravenous route. He finds that neosalvarsan possesses several advantages over the older preparation. (1) The substance is very easily soluble, making the preparation of the solution for administration much simpler. (2) The fact that sodium hydrate is not required in the preparation of the solution eliminates a number of possible dangers. (3) With similar doses, neosalvarsan is better borne than old salvarsan. Intestinal disturbances and collapse are almost never observed. (4) With neosalvarsan the dose may be increased to twice that employed with old salvarsan. Drug rashes are more frequent, but lead to no permanent injury. (5) The activity of the preparation in man certainly equals that of old salvarsan; in animals the new preparation greatly exceeds old salvarsan in potency. (6) Intramuscular injection of neosalvarsan causes much less local irritation, and the absorption is much more rapid than with old salvarsan.

Perpetual Arrhythmia.—H. A. FREUND (*Deutsch. Archiv. f. klin. Med.*, 1912, cvi, 1) reports a clinical and pathological study of cases of perpetual arrhythmia. The conclusions he arrives at are as follows: The view that perpetual arrhythmia is due to exclusion of the impulses, which normally arise in the node of Keith and Flack, is supported by Freund's findings, for all cases showed marked anatomical changes in this region. The long-continued arrhythmias probably have their origin in injury to the conduction system. The more severe the injury, the less frequent becomes the pulse. Thus a clinical syndrome may develop, which simulates closely Adams-Stokes' disease. From typical cases of Adams-Stokes' disease, such a case is distinguished by the absence of auricular systoles; the jugular vein shows the ventricular venous pulse. Possibly through severe tissue injury in the auriculoventricular region, attacks of ventricular tachycardia may arise. However, periodic auriculoventricular automatism may be present without serious disease of the auriculoventricular region. If one assumes that auricular fibrillation is the explanation of the perpetual arrhythmia, the cause of the irregularity in ventricular action is clear.

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

FORMERLY JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA AND SURGEON TO THE UNIVERSITY HOSPITAL,

AND

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL, AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

The Treatment of Nevi, Based on More than 2000 Cases.—BUNCH (*British Med. Jour.*, August 10, 1912, 296) says that during the last two years and a half he has treated over 2000 nevi by solid carbon dioxide, apart from other skin diseases. For stellate, capillary, cavernous, and flat pigmented nevi the method is excellent, and gives most satisfactory results. For linear nevus, and nevus verrucosus, where there is much thickening and warty growth, it is not so good, but these cases are, of course, very rare. For port-wine stains (*taches de feu*) it depends how far the corium and underlying structures are involved; the most satisfactory cases are port-wine stains with a nodular, irregular surface, and warty projections, and for these there is no other really satisfactory method of treatment. But for the vast majority of nevi there is no more effective treatment, satisfactory, and painless remedy, nor one which gives such uniformly good results.

A Study of Sprain Fracture as an Essential to the Occurrence of Dislocation.—Ross (*Annals of Surgery*, 1912, lvi, 599) made a study of this subject from experimental work on lower animals, and the cadaver and from *x*-ray observations. He concludes that practically all, if not all, dislocations are permitted by the primary occurrence of strain of tendons and ligaments, followed by avulsion of tendons and then sprain-fracture, or gross fracture. It is possible that some dislocations are permitted to occur by separation of the fibres of the capsule in place of by sprain-fracture or gross fracture. All dislocations should be skiagraphed, and if evidence of fracture is not found at first, pictures should be taken in many planes. All dislocations should be treated as if fracture had occurred, even in the event of negative *x*-ray evidence. Some sprain fractures are too small to be shown by *x*-ray pictures. Often there is spontaneous reduction of dislocations, and sprain-fractures or gross fracture is the only evidence left that can be detected by the *x*-rays. The sites of sprain-fractures or gross fractures provide the foci from which the osteoblasts issue, in those cases showing excessive callus or covering of joint surfaces with osseous tissue; moveover, the softer tissues found in joint cavities within a short time after the occurrence of dislocations are often in some stage of transformation into bony tissue. Sprain-fracture

or fractures occurring consistently in experimental dislocations on cadavers afford the most positive proof of the fact that dislocations are permitted to occur in this way; but failure to demonstrate sprain-fractures or fractures consistently in experimental dislocations on cadavers means nothing, since the stage to which degeneration has advanced determines whether the greater tensile strength remains in the tendons and ligaments or not. Whether the force be suddenly or slowly applied, sprain-fracture or fracture precedes the occurrence of practically all, if not all, dislocations.

Operation for Pneumatocele of the Parotid Gland and Stenson's Duct (Glass-blower's Tumor).—NARATH (*Deutsch. Zeitsch. f. Chir.*, 1912, cxix, 201) says that pneumatocele of the parotid gland and Stenson's duct gets little attention in the text-books. He reports a case which he believes is the only one to be reported up to the present time in which the condition was cured by operation. His patient had a swelling of the right cheek which had developed slowly from glass blowing, during a period of about nine years. He did not give up his work, and in 1901, about a year before Narath saw him, the inflammation extended to the mouth and increased rapidly, so that he was compelled to discontinue his work. He was admitted to Narath's clinic, November 10, 1902. On examination the orifice of Stenson's duct on the right side was distinctly larger than on the left, and the surrounding tissues were red. By pressure on the right cheek a thin fluid and air appeared. Both cheeks were rather lax, and on the left side the parotid was better defined than on the right. On blowing out his cheeks, as in his work, they became much distended, and presented a globular projection. On the right side there appeared suddenly in the region of Stenson's duct and the parotid gland, a tumor about the size of the thumb below the zygoma and opposite the lobule of the ear. When the patient stopped blowing out his cheeks, the tumor remained stationary. When it was pressed upon by the finger, it disappeared with a sound somewhat like that in an incarcerated hernia on reduction by taxis and the patient had the feeling of air and fluid entering the mouth. Stenson's duct could easily be located and probed. After the failure of conservative methods of treatment, an operation was proposed to the patient and accepted, the object of which was to reëstablish the valve mechanism at the orifice of the duct in the mouth, which was now insufficient. The peripheral half of the duct was exposed by an incision parallel to the duct, and was found to be represented by a loose sac which was easily isolated. It was ligated close to its orifice in the mouth, and divided internal to the ligature, so that the latter remained attached to the portion of the duct continuous with the gland. From the wound a probe was bored obliquely through the cheek muscles until its end made the mucous membrane of the mouth prominent. An incision was then made over the end of the probe which was passed into the mouth. The ligature attached to the free end of the duct was tied to the outside end of the probe, and the duct thus drawn into the mouth through the passage-way made by the probe. To make a better valvular closure the duct was twisted slightly on its axis and sutured to the margins of the opening in the mucosa so that its end projected into the mouth 2 to

3 mm. Healing was good and the gland condition was soon much better. But a second operation became necessary for a threatening stricture at the orifice of the duct, and was performed two months after the first. An incision was made over the duct to the parotid tissue, and the duct isolated. The gland with the duct formed only a sac which was drained externally by a rubber tube through a passage made with a slender forceps behind the lower jaw. In the following weeks an effort was made to destroy the remaining parotid tissue from which only a small quantity of secretion was exuding. One injection of alcohol and three of chloride of zinc accomplished this purpose. The fistula closed two months later, and the patient returned to work as a glass blower seven months after the second operation. He found that he could do his work better than before the operations, and had no further trouble. There resulted little or no disturbance of the facial nerve which is so frequently injured in operations on this gland.

A Contribution to Surgery of the Heart.—WAGNER (*Deutsch. Zeitsch. f. Chir.*, 1912, cxix, 221) quotes Erich Hesse as claiming, on the basis of 21 operated cases, that in 50 per cent. of all cases an exact diagnosis of heart wound was impossible. Of 7 cases seen by Wagner and operated upon in the Stettin City Hospital, in which a diagnosis of heart wound had been made before operation, the diagnosis was confirmed by the operation in only 5, and it was found that in 2 the bullet had passed by, close to the heart. A wound within the heart area does not, of necessity, indicate a heart wound, nor does the direction of the bullet always furnish a good guide. In the above 5 cases of heart wound, confirmed by operation, there were no abnormal sounds heard over the heart. Erich Hesse noted such sounds in only 1 of his 21 cases. Wagner observed an increase of the area of heart dulness in only 1 of his cases. Tamponade and strangulation of the heart is the most important symptom when it is present, but Wagner observed it only once in the 5 cases confirmed by operation, and Erich Hesse found it only 8 times in his 21 cases. Frequently the blood escapes from the pericardium through an opening into the pleural cavity. Anemia is usually present, but is not characteristic of heart wounds. The subjective symptoms of precordial distress, pain in the heart region, feeling of pressure and dyspnea, can aid in the diagnosis, but are not positive signs. Early diagnosis, therefore, is beset with difficulty, but is very important for a favorable outcome from operation. It is known that severe heart wounds can be almost symptomless. As the result of his studies, Wagner believes that as soon as a probable diagnosis of heart wound can be made, the heart should be exposed promptly, in civil life, by operation. This rule does not hold in war. He reports a case in which a heart wound was assumed to be present with certainty, and in which operation showed positively that the heart was not wounded. There was hemopericardium and hemopneumothorax, but no wound of the heart. Undoubtedly the patient would have recovered without operation. The probability is that the bullet took a course tangential to the heart, opened the pleura, and passed through the lung. Lundmark reported a case which was very similar to this one.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF APPLIED THERAPEUTICS IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

The Production of Active and Passive Immunity to the Pneumococcus with a Soluble Vaccine.—HIRSCHFELDER (*Jour. Amer. Med. Assoc.*, 1912, lix, 1373) says that the extensive employment of vaccines made from dead microörganisms has been followed by variable results. It seemed probable to him that these discrepancies might be due to the fact that in the one case an efficient quantity of the bacterial endotoxin has entered into the circulation, whereas, when no beneficial results ensued it might be that a satisfactory extract of the microörganisms had not been obtained. He made an extract by acting on living pneumococci with an alkaline pancreatin solution at 37° C. for a definite time, stopping the action by slight acidulation, and filtering through a Pasteur filter. Rabbits injected with a single dose of the extract developed relative or complete immunity to a virulent pneumococcus culture in about six or seven days. In order to determine whether it would be possible to produce a serum which would afford passive immunity, a dog was injected with increasing doses of the pneumococcus extract. The serum obtained from this dog and injected intravenously into rabbits protected them from fatal inoculations of a virulent culture of pneumococci. Unfortunately, the serum of the dog cannot be used on human beings on account of its toxicity, and experiments are being made for the purpose of producing anti-pneumococcic serum from sheep and horses. Ten patients with pneumonia were treated with the extract, and all recovered. In a majority of the cases the crisis occurred within twenty-four hours after the first dose. A striking fact was a rapid fall of the number of leukocytes within twelve hours and preceding the reduction of temperature. Hirschfelder admits that the number of the cases is far too small to warrant an estimate of the value of the treatment, but he believes that his results certainly prove that the treatment is harmless.

The Duration of Immune Bodies in the Blood after Antityphoid Inoculation. WOLLSTEIN (*Jour. Exper. Med.*, 1912, xvi, 315) found that in a series of 24 persons inoculated with antityphoid vaccine that immune bodies in the blood reached their height within two months after the first inoculation, or one month after the third inoculation, then fell rapidly within the next two months. Only 19 of the cases could be followed longer, and 8 of these were negative for bactericidins within ten months after inoculation, and 15 were negative after thirteen months. Only one serum reacted in a dilution of 1 to 1200 at the end of thirteen months. Wollstein says that there is, of course, no justification for the conclusion that clinical immunity

can be determined absolutely by the measure of immune bodies in the blood, since experience has apparently proved the contrary, a fact which can be accounted for by the latent power of the body cells to react more quickly to a stimulus which has once made them sensitive. That this power lasts for many years after an attack of typhoid fever is well known. Further study is required to prove its duration after antityphoid inoculation. It would seem, however, that reinoculation with typhoid vaccine within a year is indicated when exposure to typhoid fever seems imminent.

The Administration of Salvarsan in Syphilis.—FORDYCE (*Jour. Amer. Med. Assoc.*, 1912, lix, 1231) says that the efficiency of salvarsan bears a direct relation to the age of the infection. In the early stage three or four doses supplemented by mercury will in many cases cure the disease in from six months to a year. The florid stage requires more intensive treatment; five or six doses followed by several mercurial courses are necessary. In some forms of syphilis of the nervous system the effects of salvarsan are more satisfactory than those of mercury and potassium iodide. In malignant syphilis, when mercury has been given over a long period continuously, without changing the clinical manifestations or the blood reaction, not infrequently all of the manifestations disappear after one or two doses of salvarsan. These patients probably develop more or less immunity to mercury, or their strains of spirochetes are more amenable to arsenic treatment. A reaction uninfluenced by a long course of mercury may be changed by one or two injections of salvarsan. In other words, a combination of salvarsan and mercury is more efficient in changing the blood reaction than either alone. In the primary stage it is possible permanently to reverse the blood reaction with salvarsan, but, as the disease grows older, the probabilities of changing it with only a few doses grow less. The introduction into the system of such large quantities of the drug as is possible with neosalvarsan may so concentrate the treatment that all or most of the organisms are destroyed, but it has not yet been used long enough to enable us to draw definite conclusions.

The Effect of Benzol on Leukemia.—KORANYI (*Berlin. klin. Woch.*, 1912, xlix, 1357) reports a typical case of leukemia that improved remarkedly apparently as a result of the systematic administration of benzol. The patient was a woman, aged thirty-two years, who noticed seven months before applying for treatment, that her spleen was enlarging, and that she had become very weak. The blood count showed 3,100,000 red blood cells and 220,000 white blood cells, including 70 per cent. polynuclears, and 16 per cent. myelocytes. A single exposure to *x*-rays was made February 1, 1912, and two weeks later the benzol was commenced, giving from 3 to 4 grams a day. By April the white blood cells had dropped to 65,000, and by the middle of May to 8,000, and the general health showed marked improvement. Koranyi has tried this treatment in a number of cases of leukemia, and as yet there have been no failures. The spleen subsides to normal size in time, but there is less effect upon the lymph nodes. The benefit is more gradual than from *x*-ray therapy, but the benzol may succeed

in cases where radiation has failed to benefit. Patients who have already had *x*-ray treatment seem to respond more readily to the action of benzol. Doses of even 5 grams of benzol during the day gave rise to no serious by-effects. The stomach disturbances such as burning in the stomach, eructations, and dizziness may be avoided by giving an equal amount of oil in a capsule together with the benzol. Koranyi's attention was first called to the action of benzol upon the blood by Barker's report of three cases of purpura hemorrhagica with aplastic anemia, in 3 girls who worked with benzol in a factory. Two of these cases ended fatally. Selling's experimental research has further established that benzol first increases the production of leukocytes and then has a destructive action on them, while the number of red blood cells is not modified. At the same time it was observed that the bone marrow, the spleen, and entire lymphatic system showed marked aplasia.

Absorption of Food in Typhoid Fever.—Du Bois (*Arch. Int. Med.*, 1912, x, 177) relates the results obtained by him in a study of the absorption of the high calory diet in typhoid fever as advanced by Coleman. Du Bois found that carbohydrates when given in amounts under 300 grams a day were present in the stools only in traces, if, indeed, they were present at all. When amounts larger than 300 grams were given, the stools sometimes contained 2 or 3 grams of reducing bodies. The nitrogen of the feces averaged 1.12 grams a day, and never exceeded 1.8 grams, amounts which are within normal limits. The loss was 7.1 per cent., which is a figure lower than that of previous observers. This, perhaps, may be due to the fact that the diet was less irritating to the intestinal tract. With the fats there seemed to be a diminution of both the percentage loss and the actual weight of fat in the feces as the disease progressed. Du Bois says it is hard to give averages which are fair, but it can be said that during the first three weeks of the attack and during the height of a relapse, the patients lose on an averate 7.2 per cent. of the ingested fat. Later in the disease, with a falling temperature and decreasing toxemia, they lose about 4.5 per cent. The average loss for all cases examined was 6.02 per cent., which, though higher than the normal figure of 3 per cent. for a similar diet, is not enough higher to be of any clinical significance. The dried feces contained from 30 to 50 per cent. fat. However, very large amounts of fat were given. The stools of typhoid patients on the high calory diet resemble normal stools very closely. The indican of the urine, which is rather high during the early part of the disease, decreases steadily as the patient's condition improves. The indican excretion compares favorably with that of Folin's normal individuals. They can absorb very large amounts of fat, but the percentage of absorption is somewhat lower than normal, especially early in the disease.

The Treatment of Leukemia with Benzol.—Kiralyfi (*Wien. klin. Woch.*, 1912, xxv, 1311) reports 7 cases of leukemia treated systematically with benzol. The benzol was given in capsules together with an equal amount of olive oil, each capsule containing 0.5 gram of the drug. The dose at first was four capsules a day, and this dose was

gradually increased until the patients were taking two capsules five times a day. The length of the treatment varied from three weeks to five months. Most of the cases belonged to the myeloid type. The leukocytes returned to normal numbers and the leukemic lesions subsided. The other symptoms of leukemia showed marked benefit from the beginning of treatment. The fever and enlargement of the spleen subsided early in the course of the treatment. In the single case of lymphatic leukemia treated the improvement was noted exceptionally early, the leukocytes dropping to 7200 in three weeks, from 131,200 at first. This case had been treated a year before with the *x*-rays, with the result of a drop in the leukocytes from 80,000 to 40,000, but an increase in the glandular enlargement. The benzol treatment was also tried in a case of polycythemia with some benefit, but the patient was only under observation a short time. The results in the case suggest that possibly benzol may be of value in regulating blood production in this disease. The author states that the period of observation has been too short to determine whether the benefit will be permanent, but improvement occurred in every case treated.

PEDIATRICS

UNDER THE CHARGE OF

LOUIS STARR, M.D., AND THOMPSON S. WESTCOTT, M.D.,

OF PHILADELPHIA.

The Cutaneous Reaction to Tuberculin in Childhood.—C. PAGET LAPAGE (*British Jour. Child. Dis.*, 1912, ix, 493) states that the cutaneous method of von Pirquet is, in children, better, safer, and more reliable than the conjunctival method. The cutaneous test approximates more closely in its results to the subcutaneous, than does the conjunctival. McNeil found better results from undiluted tuberculin rubbed into the unbroken skin than when it was applied as in vaccination. Twenty-five per cent. tuberculin is strong enough to be reliable. The ordinary reaction, occurring within twelve hours, consists of redness and swelling of the area to which the tuberculin was applied, and often involves a larger area surrounding it. Rapid and ephemeral reactions occur within a few hours, reach their maximum in from ten to twelve hours, and disappear in twenty-four to forty-eight hours. Strong, lasting reactions may take two or three days in which to reach their maximum. A delayed reaction does not appear for one or two days. When it does appear it is often well-marked and may last several days or weeks. A reaction indicates that the individual has been infected with the tubercle bacillus. The body may have resisted the disease, and the tubercle bacillus be in a state of inactivity, yet the body will react to the tuberculin. The number of children reacting to the test, increase with their age, although there is probably a diminution after the tenth year. The reaction is increased by tuber-

culin treatment. It is established that there is no reaction in many cases of advanced tuberculous disease exhibiting cachexia, and in many cases of mixed infection. Slight reactions seem to occur with greater frequency in cases which are negative clinically. Prolonged reactions tend to occur in abdominal or glandular tuberculosis. McNeil claims that the intensity of the reaction varies directly with the vigor of the patient.

Pneumococcal Infection in Infancy and Childhood.—GAVIN FULTON (*Pediatrics*, 1912, xxiv, 599), in discussing pneumococcal infections in childhood reports the treatment of this condition by vaccines. The pneumococcal infection may be general from the start, and the pneumonia a local expression of it. Or the pneumococcus may invade any part of the body and be the primary factor in a local inflammation which may or may not become general. The constitutional symptoms of acute pneumococcal infection are characteristic, irrespective of the seat of the infection. There are chill, high continued fever, tachypnea, increased arterial tension, and evidence of meningeal irritation. A certain proportion of cases of pneumococcal pneumonia do not respond to the routine symptomatic treatment, there being nothing to combat the specific bacterial infection. This fact led Fulton to try out pneumococcus vaccines on a series of cases. These cases received no other treatment except the vaccine and continuous exposure to fresh air. The results in 5 cases detailed by Fulton are very good. The dose was from a half to one bulb of the vaccine containing 40,000,000. The vaccine reduced the temperature, pulse, and respiration within twenty-four hours, hastened resolution, and cut short the course of the disease. In several cases the dose of vaccine was repeated in forty-eight hours when the symptoms again tended to increase in severity, but after the second dose the symptoms became progressively less marked. Most of the cases were of the worst type, with fever of 105° to 107° F., pulse rate from 140 to 150, and respirations from 40 to 60 per minute. The ages were from three months to four and one-half years. One case died. This case was treated in the routine way at first and consent was only procured for using the vaccine after collapse had set in. Fulton believes vaccine to be a legitimate line of treatment, and of value not only in pneumonia, but in pneumococcal infection anywhere in the body. Stock vaccines were used in these cases as the delay and difficulty in preparing autogenous vaccines made this form impracticable.

The Dietetic Treatment of Purulent Affections of the Urinary Tract in Children.—HUGO NOTHMANN (*Berlin. klin. Woch.*, 1912, lxix, 1848) mentions the doubt as to the mode of infection in purulent conditions of the urinary tract in children, and suggests the probability of a hematogenous infection in many cases. Other organisms besides the bacillus coli are presumably causative factors. The latest treatment of these conditions in Germany follows an English method, and is based on the fact that in pyelitis the urine has an acid reaction. Potassium citrate is given during the whole day in large doses. Whether the results are due to the alkaline reaction induced in the urine or to flushing of the urinary tract through the diuretic action, the fact

remains that this treatment gives excellent results in pyelitis with acid urinary reaction in children. In the exhibition of alkaline waters the result is due to the alkalinity induced in the urine. Nothmann found remarkable improvement in cases of pyelitis by feeding a malt soup to the children. This diet is found to render the urine consistently alkaline, while the ordinary milk diets render it acid. Keller's "malzsuppe" was used in these cases. The original formula consists of $\frac{1}{3}$ liter milk, $\frac{2}{3}$ liter water, 100 grams "Loefflund's Malzsuppeextrakt," and 50 grams wheat flour. The presence of calcium carbonate in the malt extract accounts for the alkaline reaction of the urine. Each liter of the above formula contains 1.1 gram of calcium carbonate. This form of feeding, besides improving the urinary condition, greatly improves the general condition and nutrition of the child, and so increases its immunity against the infection. The "malzsuppe" should only be used when the child is old enough to digest this type of nourishment, and where the child's general condition indicates it. Fortunately pyelitis is not so frequent during the first six months of life, so that this form of diet should be applicable to a large number of cases occurring after the sixth month. The "malzsuppe" stimulates appetite, opposes constipation, improves the general nutrition and acts as an excellent therapeutic agent on the purulent condition of the urinary tract.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Effect of Chloral Hydrate upon the Liver and Kidneys.—HOPKINS, pathologist of the Sloane Hospital for Women, reports (*Amer. Jour. Obstet.*, April, 1912) the results of his studies from the effect produced by chloral hydrate on the liver and kidneys. He finds that occasionally this substance produces fatty changes in the liver similar to those caused by small doses of chloroform. These changes, however, are not identical with those found in eclampsia and in delayed chloroform poisoning. Chloral hydrate produces no histological changes in the kidneys, but causes an increase in the urinary nitrogen, which may be delayed until after recovery from anesthesia, and tends to return again to normal.

Fever in the Newborn.—CAUTLEY (*British Med. Jour.*, May 18, 1912) calls attention to the fact that newborn infants are exposed to septic infection at the umbilicus. Soon after birth they may show the effects of confinement in the various lesions produced by pressure or infection. Changes in the respiratory tract incident to the establishment of respiration and disturbances of digestion, may also cause

fever. The temperature of the newborn is usually depressed by bathing, and short variations in temperature are without significance. The daily rise or persistence of abnormal temperature is important. Fever occurring during the first few days after birth is usually the result of mild toxemia, which disappears with the plentiful administration of colostrum, or of water. In infants born in severe labor, pain and nervous irritation may cause fever, while meningeal hemorrhage usually produces subnormal temperature. Injury to the cranium in labor, followed by meningitis, produces fever, and where the scalp is insufficiently injured to slough, gangrene may develop and septic infection. As a rule, sepsis causes 50 per cent. of fever in the newborn. Of this, 25 per cent. may be ascribed to the digestive tract. Cautley cites the case of a mouth infection, followed by fever and death, and 1 of pustular dermatitis causing severe fever, from which the child gradually recovered. Umbilical sepsis is well recognized as a cause of fever in the newborn. The treatment of the condition consists in preventing infection by antiseptic precautions during labor, by antiseptic dressing of the cord with dry sterile powder, preceded by the application of alcohol. When infection arises chloral is sometimes useful to relieve spasms. For the toxemia, irrigation of the bowels with hot saline fluid is useful, and in severe cases saline fluid should be given beneath the skin. If the bowel movements are offensive, small doses of gray powder are beneficial. Brandy is indicated. So far as the prognosis is concerned, fever following localized infections is not a sign of great danger. Where constitutional symptoms of infection develop, the prognosis is exceedingly grave. Failure to take and to assimilate food, with great depression, are also bad symptoms. Prolonged fever, even with local or general paresis, may often end in complete recovery.

Induced Labor for Pelvic Contraction.—Bagger-Joergensen (*Archiv mensuelle l'Obstétrique*, February, 1912) reports 29 cases of induced labor in 6400 confinements, among whom were 100 cases of contracted pelvis. In 25, labor was begun by the introduction of a bougie; in 4 by rupturing the membranes. The thirty-fifth or thirty-sixth week of gestation was the time selected. There was no maternal mortality. The morbidity rate was 3.5 per cent. Of the 30 children, 27 were born living, with an immediate mortality of 10 per cent. The secondary mortality during the first year was 8 per cent.

Cleidotomy.—Leibich (*Zentralbl. f. Gynäk.*, 1912, No. 19) reports the case of a primipara brought to the hospital in labor with a large child, the mother having a normal pelvis. A general practitioner had applied forceps unsuccessfully, and in his efforts to deliver had lacerated the perineum. The head had not rotated normally and the shoulders had become impacted at the pelvic brim. The forceps had brought the head to the vulva but could not deliver. The position of the child was the second. To dislodge the shoulders cleidotomy was performed from the left side, the arm brought down, and delivery readily effected. The dead child was a male, 55 cm. long, and weighing 5050 grams. The bisacromial diameter was 14 cm., and the shoulder circumference 45 cm. The cleidotomy reduced the bisacromial

diameter to 10.5 cm. and the circumference of the shoulders to 40 cm. Examination of the body of the child showed that the subclavicular bloodvessels had not been wounded. A second case is reported in which the operation was done upon an anencephalic fetus with impaction of the shoulders. Both clavicles were severed and delivery effected by inserting a blunt hook into the right axilla. The reviewer believes that cleidotomy is often neglected in performing difficult vaginal delivery. Where the fetus is dead or dying the obstetrician should refrain from difficult extraction until he has lessened the size of the fetus. His first impulse is to perform craniotomy, but this is often not sufficient, and cleidotomy should be added. The reviewer has several times succeeded by cleidotomy followed by the application of the blunt hook in the axilla, in delivering large dead children with very little injury to the mother.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Menorrhagia of Puberty.—Weil (*Ann. de Méd. et Chir. Infantiles*, 1912, xvi, 553) says that cases of very profuse and prolonged uterine hemorrhages, occurring either coincidently with the onset of puberty, or shortly afterward, are seen not very infrequently, and have usually been attributed to some local cause, such as uterine or ovarian congestions, inflammations, or other lesions. From a careful study of several such individuals, however, Weil has come to the conclusion that the condition is, in most instances, merely one manifestation of a general dyscrasia. In 9 cases which have come under his observation no genital lesions whatever were to be found. Most of these girls had showed a clearly marked hemophilic tendency during childhood, and in 7 there was an hereditary tendency to the same condition on the maternal side. Examination of blood taken from a vein showed in every instance increased coagulation time, as did the bleeding test of Duke. This is performed by making an incision 2 mm. in length in the lobe of the ear. If the drop of blood which forms is gently removed without wiping every half minute, bleeding should cease, in a normal individual, in from two and one-half to three and one-half minutes, but in all the cases of menorrhagia at puberty this time was increased, in one instance up to one and one-half hours. In several of the cases a history of icteric attacks was present, and in one there was a remarkable family tendency to icterus. In 5 cases developmental anomalies, such as underdevelopment, gigantism, or obesity were noticeable features. Weil considers the basic trouble in all these cases to be probably some functional disturbance of all the glands of internal secretion—thyroid, pituitary, adrenals, ovaries,

etc. He thinks the hemorrhagic tendency is purpuric rather than truly hemophilic in character, as in no instance was there any evidence of paternal inheritance. He warns that these patients should be kept away from the surgeon, and considers the best treatment to be organotherapy, plus the injection of fresh, normal serum, the latter in many instances being the only thing that will stop hemorrhages which may be so severe as to threaten life. Of the various organ preparations he has found thyroid extract, given in small doses, the most satisfactory.

Lactation Associated with Ovarian Carcinoma. — Two instances of this condition are reported by SAENGER (*Monats. f. Geburts. u. Gynäk.*, 1912, xxxvi, 436). The women were aged thirty-five and fifty-five years respectively; in neither was pregnancy present. Both had showed the presence of distinct lactation before death, and at autopsy the breasts showed the histological picture of functionating organs. In one patient a primary ovarian tumor, presumably a carcinoma, had been removed seven months before death; at autopsy a condition of general carcinomatosis was found. In the second case the uterus, one ovary, and a portion of the other had been removed three years previously; autopsy showed the presence of extensive medullary carcinoma of the stomach with numerous metastases, the remaining portion of the one ovary was completely carcinomatous, and there was an adenoma of the hypophysis. Saenger calls attention to the fact that while the development of the breasts before the occurrence of pregnancy has been shown pretty conclusively to be dependent upon the presence of healthy ovaries, the relations between these structures during pregnancy are by no means so constant, nor are the causes of the not infrequently observed phenomenon of extra-gestational milk secretion thoroughly understood. Such instances have been described in connection with ovarian cysts, and other ovarian tumors, but, so far as he could determine, not in connection with carcinomas. It is well known that occasionally lactation appears after double oöphorectomy, and cases are on record where normal lactation followed castration during pregnancy, so that the presence of the ovaries cannot be considered necessary to its occurrence. In the 2 cases reported by Saenger, however, castration cannot have been the only factor, as in one a portion of one ovary was not removed. Saenger considers the presence of the developing tumor to have been the underlying cause of the lactation in these instances, accepting the theory of Askanazy that embryonal tumors, such as teratomas, can have a specific action on the genital sphere, and that other tumors with but slightly differentiated, embryonic cells—anaplastic carcinomas and sarcomas—can exercise a similar stimulus to hyperplasia of certain organs. Saenger believes that carcinomas developing in the ovary may be especially embryonic in character, and that the unripeness of the tumor, rather than its seat in the ovary, is responsible for its ability to cause changes in distant organs—changes which have manifested themselves not only by the assumption of physiological activity on the part of the breasts, but, in one instance, by the adenomatous proliferation of the hypophysis as well.

Lactic Acid Therapy in Gynecology.—Pouliot (*Rev. prat. d'Obst. et de Gyn.*, 1912, xx, 257) says that while the internal use of lactic acid bacilli is falling off somewhat since the first burst of enthusiasm, the value of these organisms under certain conditions for external application is just beginning to be realized. Lactic acid cultures are not of much use in combatting acute suppurative conditions, but in infections by members of the colon group, by most of the anaërobes, and especially by the organisms of putrefaction, their antagonistic properties may be utilized to great advantage. For local application liquid cultures are, of course, the best, next to these the powdered "lactobacilline." The compressed tablets Pouliot believes to be often inert, as they may be rendered sterile by the heat engendered during compression. While the use of this form of therapy in gynecology is of distinctly limited application, Pouliot has found it of decided value in the treatment of suitable conditions. He gives vaginal injections of the liquid culture in cases of ulcerated neoplasms of the cervix, necrotic polyps, esthiomène vulvæ, vaginismus (which he considers to be always accompanied by an ulceration, or at least a fissure of the vestibule), and after vaginal hysterectomy by the clamp method, to combat the fetid discharge which always results from necrosis of the pedicles.

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,

PHILADELPHIA.

On Ocular Palsies Occurring as the Sole or Most Conspicuous Evidence of Disease. — Hawthorne (*Ophthalmoscope*, November, 1911, p. 750) discusses the important question whether in a given case of palsy of ocular muscles, the condition may be regarded as simply a local matter, or whether it is an indication, perhaps the first, of progressive and serious disease of the central nervous system. Probability there may be, one way or the other, but not certainty, or at least certainty only arrives when, through the lapse of time, it is seen that the paralysis was a mere isolated event in the patient's clinical history, or that, on the contrary, it was the forerunner of even more serious mischief. Analogously to disturbances of other peripheral nerves, for example, the facial, palsies of one or more of the ocular muscles may undoubtedly be a purely local phenomenon. The difficult is to be sure that this is the explanation in any individual case. All that can be said, perhaps, in the way of help in this difficulty is, that if the absence of syphilis can be guaranteed, if there are no

other signs of nervous disease, and if the patient is more or less definitely "rheumatic," it is a reasonable conclusion for practical purposes that the paralysis is of the simple order. Not that this necessarily means that it is to be of brief duration or that a complete cure is certain; on the contrary some of the ocular paralyses associated with central organic disease are but slight in degree and transitory in duration. One remark in reference to the simple or rheumatic paralyses may be added: It is that for the most part such paralyses are confined either to a single nerve or to a single branch, or possibly neighboring branches, of one and the same nerve. This rule is not absolute, but it has a fairly commanding range. Of ocular paralyses connected with chronic degenerative nervous disease the relation with tabes dorsalis is of great importance, not only because such paralyses may accompany the other symptoms of the affection, but from the fact that the ocular disturbance may be the first, and for some time the only evidence of those degenerative changes in the nervous system, which in their complete expansion produce the clinical picture of tabes dorsalis. And what is true of tabes is almost equally applicable to its near relation—general paralysis of the insane. Another nervous disease, of which ocular paralysis may be the first symptom, is disseminated sclerosis. Syringomyelia may also include an ocular paralysis among its symptoms, and so occasionally may chronic bulbar disease. In gross intracranial lesions ocular palsies not infrequently occur, but here for the most part there are other and equally conspicuous symptoms. Among intracranial lesions capable of producing ocular palsies may be mentioned polio-encephalitis superior. Chlorosis and otitis media are also occasionally accompanied by paralysis of the sixth cranial nerve. In both of which diseases double optic neuritis may also be present. The important point clinically, is to appreciate the fact that even so terrifying a combination as an ocular paralysis with double optic neuritis does not necessarily mean serious intracranial disease and a correspondingly anxious prognosis.

Pathogenesis of Glaucoma.—Fricker (*Klin. Monatsbl. f. Augenheilk.*, June, 1912, p. 723) has examined 30 cases of glaucoma (mostly glaucoma simplex) with reference to the blood pressure. This was usually determined by the method of von Recklinghausen, occasionally by that of Riva-Rocci and thence converted to the von Recklinghausen values. Of these 30 cases, 20 males and 10 females, in 4 the heart, bloodvessels, lungs, and kidneys were healthy; 1 had tabes. In these 4 cases the average pressure was 150 (von Recklinghausen), that is, the highest limit in health. In 3 cases, aside from an exceptionally high blood pressure averaging 210 (v. R.), no definite pathological condition was found, although the excessive pressure rendered probable the presence of some obstacle to the circulation. Arteriosclerosis alone was present in 10 cases averaging 195 (v. R.) pressure; of these, 5 showed dilatation of the left heart upon the radiograph and 3 a widened shadow of the trunk of the aorta. Death took place in 2 of these cases, with symptoms of cardiac insufficiency. Arteriosclerosis and interstitial nephritis, with tension averaging 205 (v. R.), was found in 6 cases. Arteriosclerosis and emphysema with tension 185 (v. R.) was observed in 3 cases, and emphysema alone, tension 180 (v. R.),

in 3. Arteriosclerosis with myocarditis, tension 150 (v. R.), was found in 1 case. The great preponderance of arteriosclerosis alone or in combination with lesions of the heart, lung, or kidneys is very striking in this series. If the case with tabes be excepted, no other disease was present; while arteriosclerosis cannot be assumed to be the sole cause of glaucoma, it should be carefully searched for in every case, and if found, the proper treatment should receive serious consideration.

Voluntary Nystagmus.—ELLIOT (*Ophthalmoscope*, February, 1912, p. 70) observed in a healthy young man with normal vision the ability to produce voluntary nystagmus; to do so, the subject stares straight in front of him, and within a second or two the phenomenon begins. It is a binocular horizontal oscillatory movement; the amplitude is large, and the movements too rapid to count. The oscillations cease when the effort is relaxed. There is a feeling of weariness and lateral distortion of the objects during the movements. Of recent years the nystagmus has commenced spontaneously on several occasions, but has been readily controllable.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL.

Hypogenetic Nephritis.—JIANU and MELLER (*Cent. f. allg. Path. u. path. Anat.*, September 15, 1912) detail a case of what has been called hypogenetic nephritis, a term instituted by Babes to describe nephritis in a hypoplastic kidney. A considerable number of cases has been shown, the clinical characteristics being a rapid nephritis of two or three days' duration, with uremic manifestations in a patient attacked by some relatively mild disease, such as bronchitis or influenza. Jianu and Meller's case is characteristic, showing a man, aged twenty-five years, who suffered from a diarrheic attack and died in uremic coma. The kidneys weighed 50 and 55 grams respectively, and were lax and soft; considerable uniform fibrosis and relative diminution of glomeruli were observed, while the moderately damaged tubules showed signs of attempts at regeneration. Such kidneys are from the first insufficient, and suffice only for the daily needs of the body under normal conditions; when there is laid upon them the necessity to excrete in addition even mild toxins, they prove inadequate, are damaged, and the body enters into a state of toxemia so great and so cumulative as to cause death. This toxemia, or the agents which cause it, is responsible for the inflammatory changes that are to be

seen. Such a case could present only academic interest to the practitioner were it not for the fact that the subject, in common with the other reported cases, showed other abnormalities in the direction of hypoplasia; these are oftenest in the formation of the genitalia, and Jianu and Meller deduce the conclusion that the presence of hypoplastic abnormality of the genitalia should forewarn the physician of the possibility of the existence of incompetent kidneys.

Tumors in Cold-blooded Animals.—PLEHU (*Wien. klin. Woch.*, 1912, No. 19) reviews the subject of tumor formation in cold-blooded animals, pointing out that as in the warm-blooded, different forms of carcinoma and sarcoma are found, as well as other forms of neoplasm, the nervous system as yet being the only set of organs that has not been found implicated. Carcinoma is essentially a disease of the old, while sarcoma, a much rarer form of tumor, is not so. Metastasia is infrequent, and this especially so in the case of sarcoma. Plehu considers the erratic growth of cells in the *anlagen* of embryonic organs as the most frequent site of neoplastic growth, but gives instances also of its development in scars. As a causative agent, parasites are not to be considered, although their ability to cause hyperplastic overgrowth is undeniable, a distinction which appears to the reader to be insufficiently proved.

A New Recorder in Wireless Telegraphy.—CH. LEFEUVRE (*Jour. de Physiol. et de Path. gén.*, September, 1912, xiv, No. 5) publishes a strange addition to the literature of wireless telegraphy by showing that he has transcribed, in terms of the longer and shorter muscular movements of the nerve-muscle preparation in the frog, messages sent out from the Eiffel tower at certain fixed times. The spools of a telephonic receiver are used, and currents are induced in the nerve-muscle. The simple apparatus required is shown, as well as the tracings, which indicate by long and short contractions the dashes and dots of the Morse alphabet The experiments were made at Rennes, about 180 miles from Paris. This strange thing shows the extreme sensibility of the nerve-muscle preparation as a galvanoscope; and it is worth noting that, despite many attempts, no one has yet succeeded in making a satisfactory apparatus for graphic reproduction of the messages received by wireless, such being still taken by sound in telephonic instruments.

Changes in the Liver after Parathyroidectomy.—MOREL and RATHERY (*Jour. de Physiol. et de Path. gén.*, September, 1912, xiv, No. 5) describe with greater certainty than has yet been done the hepatic lesions that follow parathyroidectomy, which they find constantly present. The intensity of these lesions does not depend on the time that elapses after the removal of the parathyroids, and the simultaneous removal of thyroid tissue does not affect them; hemorrhages in the liver are not marked, nor do they occur with constancy, and the amount of fat in degenerated areas, depending upon the alimentation of the animal, varies widely. The cellular changes observed consist of the appearance of areas of homogeneous degeneration of the protoplasm, modifications in number and form of the fuchsin-staining granules, fragmentation and granule formation in the protoplasm, and

on one occasion, cytolysis. These marks of acidosis were practically reproduced by the intravenous injection of less than fatal amounts of ammonium carbonate.

Comparative Toxicity of Methyl and Ethyl Alcohol.—The occurrence of large numbers of fatal cases of methyl alcohol poisoning gives interest to the experiments of NICLOUX and PLACET (*Jour. de Phys. et de Path. gén.*, September, 1912, xiv, No. 5), with regard to its toxicity in comparison with ethyl alcohol. In a single large dose given intravenously methyl alcohol is the less toxic, but at death there is a greater proportion found in the blood and the tissues; of the tissues, the brain is the most avid in fixing either form of alcohol. If the alcohol be ingested and in repeated doses, methyl alcohol is the more toxic, because it is capable of less complete combustion, and is eliminated more slowly; a quarter of the methyl alcohol ingested is found in the excretions and the excretory organs. In spite of these facts, Nicloux and Placet consider that it is necessary to invoke the impurities of methyl alcohol to explain the numerous fatal cases unless it can be proved that man has a particular susceptibility to the action of the drug.

The Lesion in Whooping Cough.—MALLORY and HORNOR (*Jour. Med. Research*, November, 1912, xxvii, No. 2) were fortunate enough to obtain material from 3 cases dying of whooping cough, and to be able to observe the lesions in the trachea and the bronchi. The bacillus which they found is probably identical with that described by Bordet and Gengou, and the chief interest of their observations lies in the fact that the bacteria are found in large numbers between the cilia of the epithelial cells, lying thus on the surface. The cilia are interfered with and perhaps even destroyed; the normal removal of secretion is prevented and the respiratory surface kept continuously irritated, so that cough is produced. The toxic effects of the bacillus, while undeniable, are, nevertheless, relatively unimportant.

The Serum Diagnosis of Echinococcus Infection.—B. HAHN (*Münch. med. Woch.*, 1912, No. 27) has conducted experiments in the serum diagnosis of echinococcus according to the complement-fixation method of Ghedini, and considers it an effective method for infection by Tænia echinococcus or Tænia saginata, although he admits that now and then a definitely infected case shows a negative result. The most effective antigen is watery bladder-washing, freshly used. Watery extract of echinococcus or of saginata is utilized. Notwithstanding this scientific advance, it is likely that the visual method will remain the favorite means of diagnosis for some time to come.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this* JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *provided the request for them be written on the manuscript.*

All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1927 Chestnut St., Phila., Pa., U. S. A.

JAN

VOL. C

A
T

SOME
LA

THE R
VA

CHRON
ELS

THE
MIL

DIAPH

SOME
EN

THE T
By

THE R
Ph

A CLIN
O

SOME
By

PRIMA
L

Phil

COPYRIG